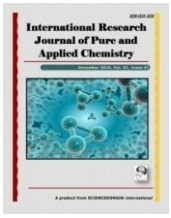

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Novel Salts of Sunitinib an Anticancer Drug with Improved Solubility

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Polymorph, co-crystal and salt screening experiments were carried out to identify novel solid forms with the improved physicochemical properties, particularly water solubility in the present case. Co-crystal formation was evaluated with urea and nicotinamide. These coformers do not have any ionic groups that favor the formation of salts. Sunitinib malate salt is being currently sold in the market. It is poorly soluble in water. Salt screening experiments were conducted with adipic acid, glutaric acid, nicotinic acid, 4-hydroxy benzoic acid and saccharin. The salts with 1:1 ratios were obtained with these acids, except for adipic acid, which yielded a 2:1 solid form. The solubility of these salts in deionized water was found to be 6 to 10 times greater than that of the marketed salt (sunitinib malate).

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Reversible Z-E isomerization was also well thought-out especially in presence of light and the isomerization was checked by HPLC. Formation of undesired E-isomer was additionally confirmed by ^{1}H NMR. This observation has implications in the solubility study of sunitinib salt samples using HPLC method.

Keywords: Sunitinib; photosensitive; novel salts; conformers; solubility; HPLC.

1. INTRODUCTION

An important goal of solid-state pharmaceutical development is to increase drug solubility while maintaining a stable form. This objective is critical because solubility and permeability are the major factors used to describe oral absorption according to the biopharmaceutics classification system (BCS). The use of salts in the pharmaceutical industry is a well-known fact. Salts modify properties of the solid forms such as melting temperature, solubility, stability, dissolution rate and bioavailability without altering the desired effect of drug [1]. Salt formation is essentially a three component system involving an acid (A), a base (B) and one or more solvents. A salt is formed by the transfer of a proton (H^+) from an acid (A) to a base (B): A-H + B → (A^-) (B^+-H). In order to assist salt selection a number of empirical rules have been proposed, such as the 'rule of three'. This states that salt formation generally requires a difference of at least three pK_a units between the conjugate base and the conjugate acid, pK_a (Base) - pK_a (Acid) ≥ 3, where pK_a is the ability of an ionisable group to donate a proton (H^+) in an aqueous medium and is often referred to as the dissociation constant. When the difference is ≤ 3, the product can be either salt or co-crystal.

API co-crystals, like API salts, have demonstrated the ability to modify physicochemical properties of the APIs [2a-f]. Cocrystals can be made for nonionizable drugs, which are restricted from salt formation. Also, for ionizable drugs, the number of suitable cocrystal ligands (i.e. coformers) can exceed the number of suitable counter ions. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent [3]. If the incorporated solvent is water, the solvate is commonly known as a hydrate. Different polymorphs of a given crystalline compound (salt or co-crystal) can have different physicochemical properties [4]. Systematic screening for polymorphs has therefore become an essential step in drug development to select a factual form in order to avoid problems caused by polymorphic transitions during processing. [5] The crystallization of polymorphs can be affected by numerous factors, which include, the nature of solvents [6a-d] and the presence of polymers [7] or other additives [8].

Sunitinib is a new vascular endothelial growth factor receptor inhibitor, has demonstrated high activity in renal cell carcinoma (RCC) and is now extensively used for patients with metastatic disease [9,10]. It is sold as malate salt by Pfizer under the brand name Sutent. Sunitinib is a yellow to orange powder with solubility of 25 mg/ml in acidic solutions (pH 1.2 - 6.8) [11] and 10-50 μM in plain water. The solubility of sunitinib rapidly decreases at pH greater than 6.8. Hence Sunitinib malate may be considered class III drug, a high solubility and a low permeability compound according to the biopharmaceutical classification. Consequently there is a need to obtain new salts of sunitinib with improved water solubility, though several salts have already been identified for this API [12,13] (Scheme 1).

Sunitinib molecule has an exocyclic double bond at 3-position of the oxindole ring and consequently it can exhibit Z-E isomerism. Anand and Narmada have revealed that SU5416, closely related to sunitinib, undergoes photo induced conversion into the less stable E isomer in solution [14] (Scheme 2). Present study deals with the synthesis of sunitinib, Z-E isomerization and identification of novel salts with improved water solubility.

2. MATERIALS AND METHODS

All the key intermediates for synthesis of sunitinib were procured from Shanghai Parling pharma co. ltd. China. Solvents and reagents were used by way of, obtained from Rankem, Qualigens and Ranbaxy Labs. Ltd., India. Waters HPLC 2695 alliance separation module (with customized syringe and loop volume of 2.5 mL) with PDA 2998 detector was used for investigation. Perkin Elmer CHNS/O analyzer 2400 was used for CHN analysis. Melting point was recorded on Buchi b 545. IR spectra were recorded on Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H NMR spectra was recorded in DMSO-d_6 at 400 MHz

using TMS as an internal standard. Mass/Ms-Ms data was generated by using QTRAP LC/MS/MS system (Applied Biosystems). The XRPD of the samples were determined by using Instrument: PANalytical; Model X'pert PRO; Detector: X'celerator; Scan Range: 3-40; Step size: 0.02; Range: 3-40 degree 2 theta; CuKα radiation at 45 kV and 40 mA. DSC of the samples was determined by using Mettler-Toledo 821e. Data collection parameters: Scanning rate: 10 ºC/min; Temperature: 30 ºC to 300 ºC. TGA of the samples were determined by using TA Q500 between 30 ºC to 300 ºC at 10 ºC/min scan rate. In the Z-E isomerization studies, the solutions (in 100 ml volumetric flasks) - prepared by means of dissolving 25 mg of sunitinib in 100 ml of each solvent - were either directly exposed to halogen lamp (150 W) or sunlight.

3. EXPERIMENTAL

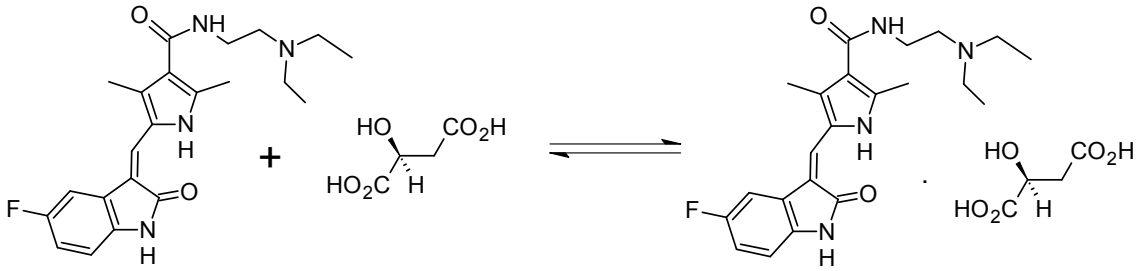
3.1 Z-E Isomerization

Photo induced Z-E isomerization study in sunitinib molecule was carried out by HPLC method using Kromasil C_8 (250 × 4.6 mm; 5 µm particle size) (procured from Akzonobel) stationary phase. The gradient elution consisted of potassium dihydrogen orthophosphate buffer (pH 4.5) and acetonitrile (1:1 v/v) with an injection volume and flow rate of 5 µl and 1 ml/min, respectively with detection wavelength 210 nm. This transformation of desired Z-isomer into unstable E-isomer was moreover proved by ^{1}H NMR of compound in DMSO-d_6 after going on exposure to light. Pure Z-Isomer ^{1}H NMR (400 MHz, DMSO): δ 0.98 (6 H, t, C27, 29-H_a), 2.43 (3H, s, C21-H_a, 2.45 (3H, s, C18-$H_{a)}$, 2.47-2.57 (*6H, m, C28, 26, 24-H_a), 3.27-3.34 (2H, m, C23-H_a), 6.83-6.86 (1H, m, Ar-H_a), 6.90-6.95 (1H, m, Ar-H), 7.43 (1H, t, N22-H_a), 7.71 (1H,s, C11a-H_{aa}), 7.75 (1H, d, Ar-H), 10.89 (1H, s, N-H), 13.68 (1H, s, N-H).

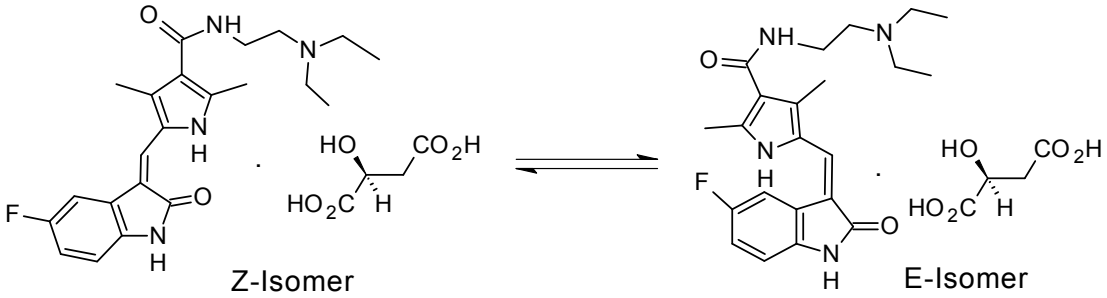
When Z-Isomer exposed to sunlight for 4 hours (E-Isomer) ^{1}H NMR (400 MHz, DMSO): δ 1.00 (6 H, t, C27, 29-H_b), 2.21 (3H, s, C21-H_b), 2.43-2.45 (3H, s, C18-H_b), 2.51-2.55 (*6H, m, C28, 26, 24-H_b), 3.27-3.30 (2H, m, C23-H_b), 6.81-6.86 (1H, m, Ar-H_b), 6.99-7.04 (1H, m, Ar-H_b), 7.34 (1H, d, Ar-H_b), 7.37-7.43.

3.2 Solubility Data

The equilibrium solubility study of sunitinib salts in DI (Deionized water) water was carried out by using gradient elution HPLC method consisted of potassium dihydrogen orthophosphate buffer (pH 6.5) and acetonitrile-MeOH mixture (1:1 v/v) with an injection volume and flow rate of 10 µl and 0.75 ml/min on Kromasil C_8 column (250 × 4.6 mm; 5 µm particle size), respectively through detection at 270 nm.



Scheme 1. Scheme for the synthesis of sunitinib Malate



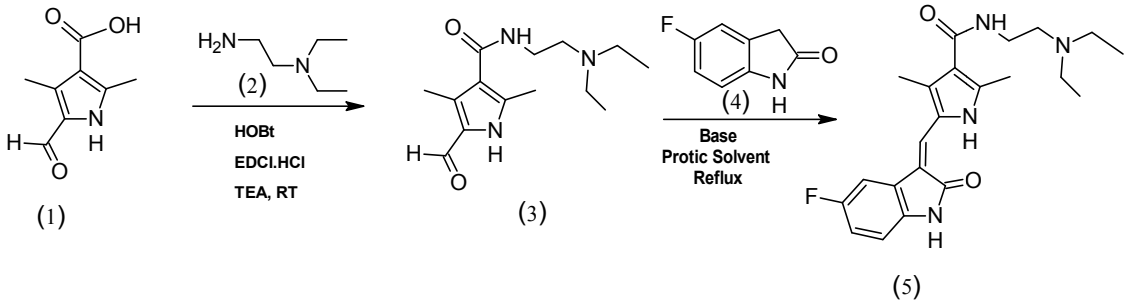
Scheme 2. Z-E Isomers of sunitinib malate

3.3 Sunitinib Synthesis

Sunitinib was prepared in two steps from imidazole derivative (1) as per the reported procedure (Scheme 3) [15]. Amidation of 1 with diethylethylenediamine (2) in presence of EDCI.HCl (N-Ethyl-N′-(3-dimethylaminopropyl) carbodiimidehydrochloride), HOBt (Hydroxybenzotriazole) and TEA (triethylamine) at RT yielded imidazole-amide derivative (3). Intermediate 3 was then and there condensed with oxindole derivative (4) in presence of base in protic solvent to give crude sunitinib (5) in quantitative yields. The crude sunitinib (5) was then purified via acid-base treatment as reported earlier [16]. The spectra's of synthesized compound shown in supporting information (S4 to S9).

3.4 Solid form Screening

Polymorph screening was carried out by treating sunitinib with L(-) malic acid (in 1:1.05 molar ratio) in 4 volumes of various solvents at room temperature (RT) for about 16 hours and stirring the malate salt in 4 volumes of numerous solvents at RT for about 10-12 hours. Co-crystal formation was assessed with two coformers, namely urea and nicotinamide. 1:1 molar ratio of the components was suspended in MeOH (methanol) and CH_3CN (acetonitrile), in addition stirred the mixtures at RT for about 16 hours. Salt screening was carried out with various



Scheme 3. Scheme for the synthesis of sunitinib

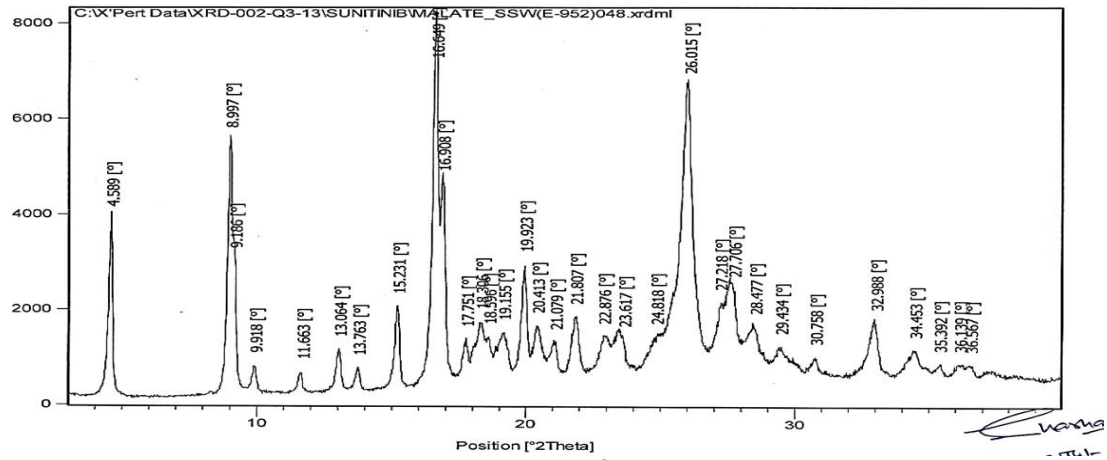


Fig. 1. XRD spectrum of sunitinib Base

M. P.: 216.6 °C, IR (KBr) V_{max}(in cm^{-1}): 3424, 3339, 3042, 2955, 2470, 1968, 1870, 1675, 1637, 1563, 1194, 1520, 1476, 1463, 1440, 1377, 1322, 1286, 1253, 1193, 1151, 1096, 1071, 1047, 800, 666 and 586. ^{1}H NMR (400 MHz, DMSO): δ 1.00 (6 H, t, C27, 29-H, J = 7.1 Hz), 2.43 (3H, s, C21-H, 2.45 (3H, s, C18-H, 2.55-2.62 (6H, m, C28, 26, 24-H), 3.29-3.34 (2H, m, C23-H), 6.83-6.86 (1H, m, Ar-H), 6.90-6.95 (1H, m, Ar-H), 7.47 (1H, t, N22-H), 7.72 (1H, s, C11a-H), 7.76 (1H, d, Ar-H, J =9.4 Hz), 10.90 (1H, s, N-H), 13.69 (1H, s, N-H),); ^{13}C NMR (100.6 MHz, $CDCl_3$): 15.82, 17.06, 18.56, 42.17, 51.74, 56.87, 111.12, 115.20, 117.56, 119.82, 125.93, 130.07, 131.02, 132.38, 135.36, 139.73, 141.79, 162.29, 169.73 (CO), 174.79 (CO). Mass: 398.4 [M + H]$^+$, 399.3; MS/MS: 326.1, 283.1, CHN: C-65.90, H-7.12, N-13.94. Theoretical CHN: C (66.31%), H (6.83), F (4.77%), N (14.06%), O (8.03%), DSC: Single endotherm at 234.37 °C, TGA: No significant weight loss and X-ray powder diffraction (XRPD) peak pattern is depicted in Fig. 1 indicates the obtained sunitinib base is a crystalline solid

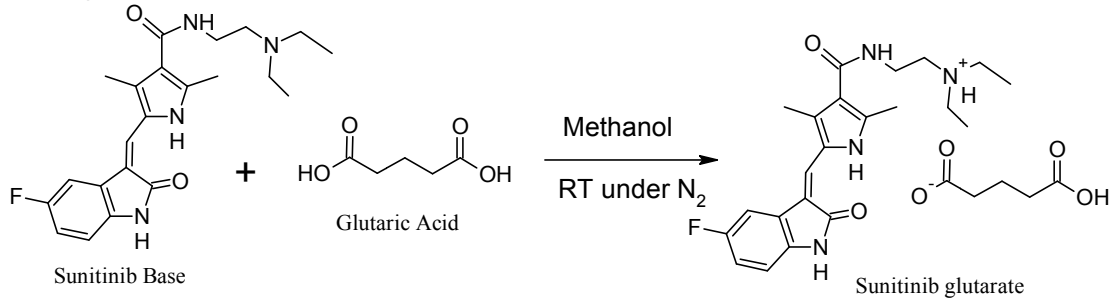
organic acids such as adipic acid, glutaric acid, nicotinic acid, 4-hydroxybenzic acid and saccharin. Mixtures of sunitinib and salt-former (in 1:1.05 molar ratio) were stirred in 10-15 volumes of MeOH (methanol) or acetonitrile at RT for about 12-16 hours and the resulting solutions either clear or suspensions were further cooled down to 0-5 ºC and stirred at 0-5 ºC for about 1 hour before filtration. In all the above cases the solids were separated from the solvent through vacuum filtration and dried them at 45-50 ºC under vacuum for about 10-15 hours, scheme 4 to 8.

3.4.1 Sunitinib Glutarate

5.0 g of Sunitinib base was suspended in 75 ml of methanol at RT under N_2. 1.82 g of glutaric acid (1.1 meq) was added to the mixture at RT. The mixture was stirred at RT for about 16 hours and then cooled down to 0-5 ^{o}C and stirred at this temperature for 1 hour. Red colored solids were collected by vacuum filtration and washed the material with 25 ml of methanol. Dried the product under vacuum at 50 ^{o}C temperature for 12 to 14 h. The crystalline Form I of glutarate salt of sunitinib (scheme 4) was obtained and characterized by X-ray powder diffraction (XRPD) peaks pattern substantially as depicted in Fig. 2.

3.4.2 Sunitinib Adipate

5.0 g of Sunitinib base and 2.0 g of adipic acid (1.1 meq) were suspended in 75 ml of methanol at RT under N_2. The resulting mixture was stirred for 5 hours at RT. The red colored solids were collected by vacuum filtration and washed with 50 ml of methanol at RT. Dried the product under vacuum at 50 ^{o}C for 12 to 14 h. The crystalline Form I of adipate salt of sunitinib (scheme 5) was characterized by XRPD peak pattern substantially as shown in Fig. 3.



Scheme 4. Scheme for the synthesis of sunitinib glutarate

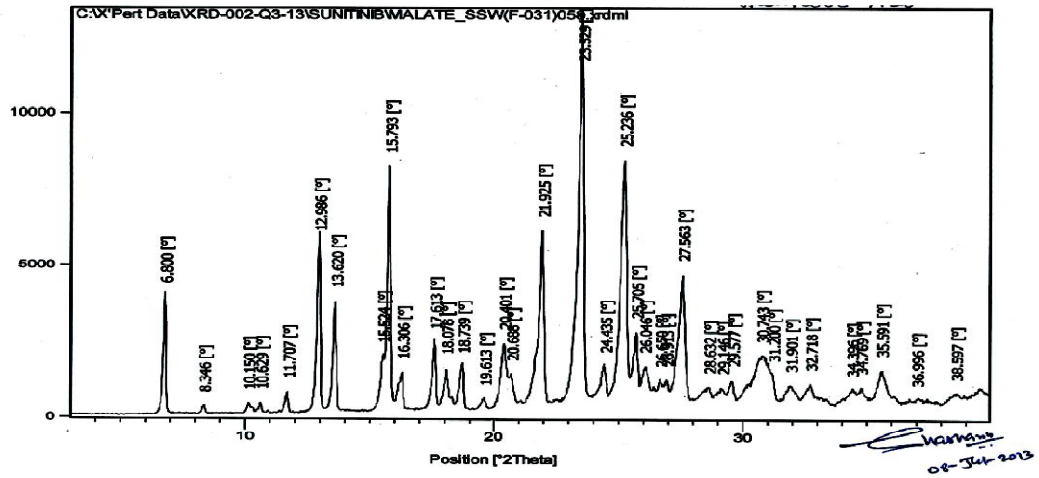


Fig. 2. XRD spectrum of sunitinib glutarate

% Yield = 88, M. P. = 204.2^{o}C, IR (KBr) V_{max}(in cm^{-1}): 3427, 3189, 3047, 2987, 2203, 1679, 1628, 1572, 1525, 1326, 1194, 1179, 697, 666, and 588. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (6 H, t, C29, 27-H, J = 7.08, 7.12), 1.69 (2H, p, C34-H, J = 7.44 Hz), 2.23 (4H, t, C33, 35-H, J = 7.04 Hz), 2.43 (6H, d, C18, 21-H, J = 7.8 Hz), 2.50-2.60 (6H, m, C24, 26, 28-H), 3.27-3.32 (2H, C23-H, m), 6.85 (1H, d, Ar-H, J = 4.6 Hz), 6.94 (1H, d, Ar-H, J = 8.48 Hz), 7.44 (1H, t, N22-H, J = 5.52, 5.56 Hz), 7.71 (1H, s, C11a-H), 7.74 (1H, d, Ar-H, J = 9.4 Hz), 10.88 (1H, s, N13-H),13.68 (1H, s, N1-H), DSC: Single endotherm at 202.38 ^{o}C, TGA: No significant weight loss

3.4.3 Sunitinib 4-hydroxy benzoate

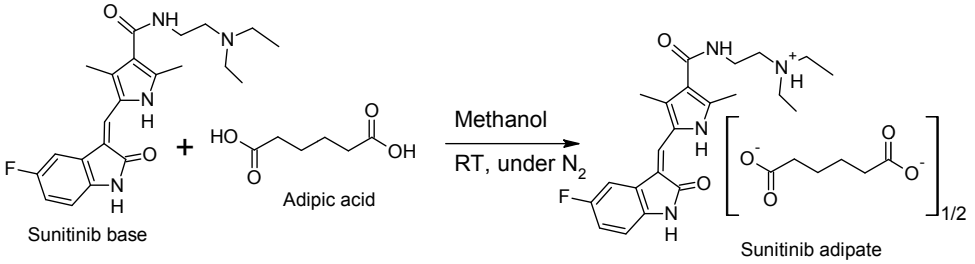
5.0 g of Sunitinib base and 1.90 g of 4-hydroxybenzoic acid (1 meq) were suspended in 75 ml of methanol under N_2 and stirred at RT for 16 hours. Cooled the mixture to about 10 ºC and stirred at this temperature for 1 hour. Orange colored material was collected by filtration and washed with 25.0 ml of MeOH (methanol). Dried the product under vacuum at 50 ºC for 12 to 14 h. The crystalline Form I of 4-hydroxybenzoate salt of sunitinib (scheme 6) is characterized by XRPD peak pattern substantially as depicted in Fig. 4.

3.4.4 Sunitinib Nicotinate

5.0 g of Sunitinib base and 1.69 g of nicotinic acid (1.1 meq) were suspended in 50 ml of methanol at room temperature under N_2 and stirred the resulting mixture at RT for 16 hours. Cooled down the solution to 10 ºC and stirred the reaction mixture for 1 hour at equal temperature. The orange solids were filtered, washed with 25 ml of methanol and dried 50 ºC for 12 to 14 h under vacuum. The crystalline Form I of nicotinate salt of sunitinib (scheme 7) is characterized by XRPD peak pattern significantly as depicted in Fig. 5.

3.4.5 Sunitinib Saccharate

5.0 g of Sunitinib base was suspended in 75 ml of acetonitrile at room temperature under N_2. Charged 2.52 g of Saccharin (1 meq) at RT. After 5 to 10 minutes the mixture became dense paste. Additional 20 ml acetonitrile was added to it and stirred at RT for 16 h. The orange solids were filtered, washed with 25 ml of acetonitrile and dried the product under vacuum at 50 ^{o}C for 12 to 14 h. The crystalline Form I of saccharate salt of sunitinib (scheme 8) is characterized by XRPD peak pattern substantially as represented in Fig. 6.



Scheme 5. Scheme for the synthesis of Sunitinib adipate

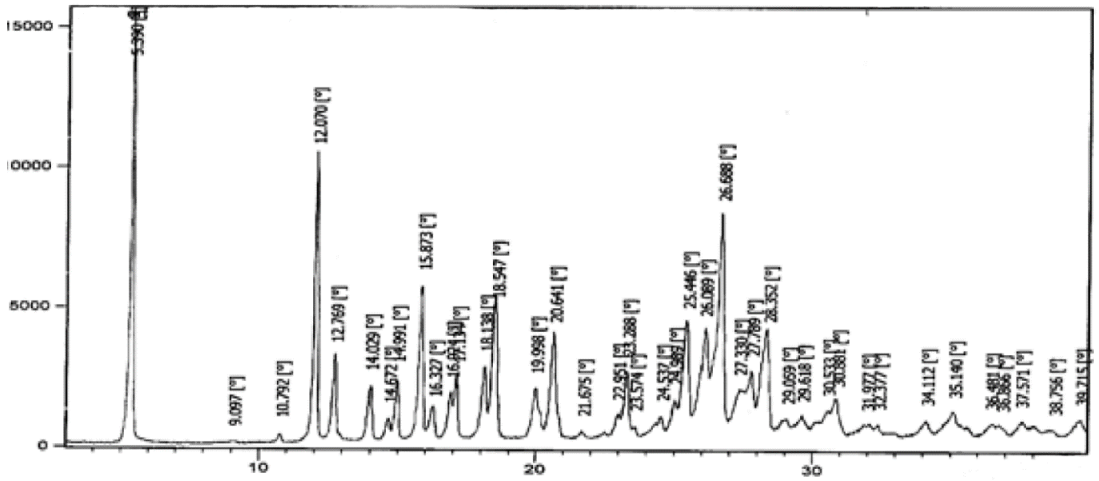
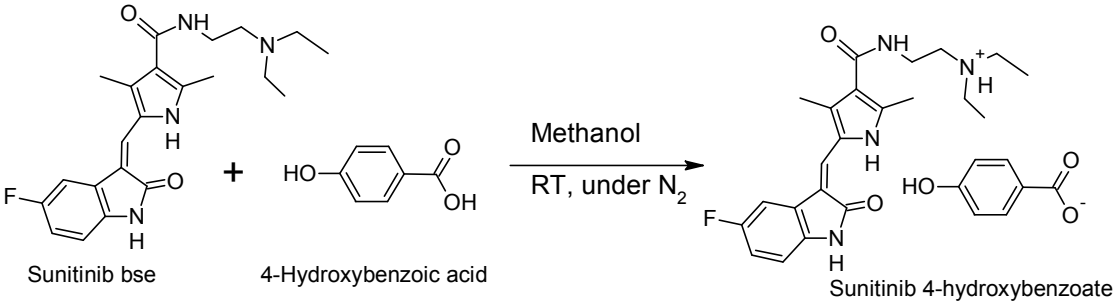


Fig. 3. XRD spectrum of sunitinib adiate

% Yield = 70.3, M. P. = 200.0^{o}C, IR (KBr) V_{max}(in cm^{-1}): 3230, 2952, 1680, 1627, 1588, 1527, 1479, 1328, 1147, 667 and 588. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (6H, t, C27, 29-H, J = 7.08, 7.12 Hz), 1.50 (2H, m, C34, 35-H), 2.20 (2H, m, C33, 36-H), 2.42-2.56 (12 H, m, C18, 21, C24, 26, 28-H), 3.26-3.31 (2H, m, C23-H), 6.84 (1H, d, Ar-H, J = 8.4 Hz), 6.90-6.95 (1H, m, Ar-H), 7.43 (1H, t, N-H), 7.71 (1H, s, C11-H), 7.76 (1H, d, Ar-H, J = 9.4 Hz), 10.88 (1H, s, N-H), 13.68 (1H, s, N-H) DSC: Endotherms at 184.3 and 207.4 ºC, TGA: No significant weight loss



Scheme 6. Scheme for the synthesis of sunitinib 4-hydroxy benzoate

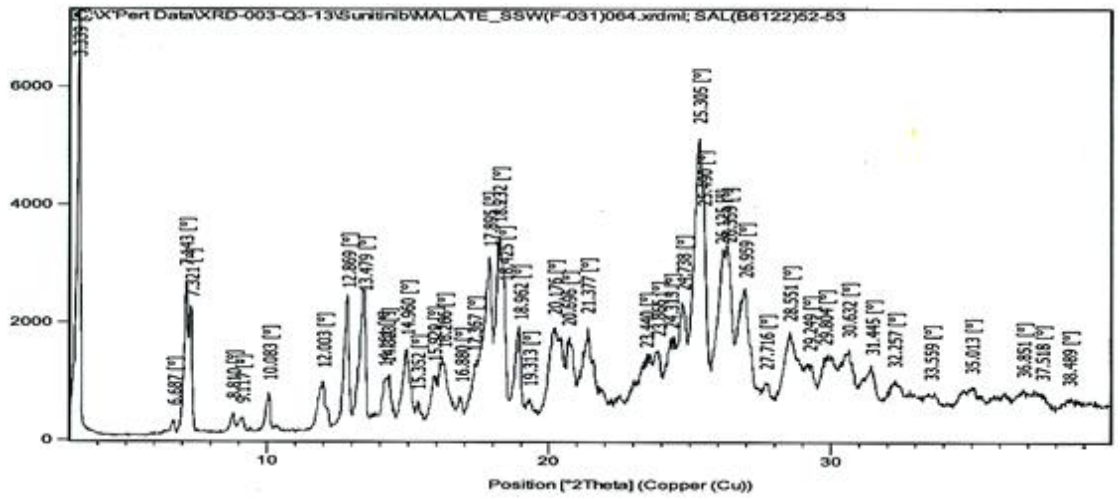
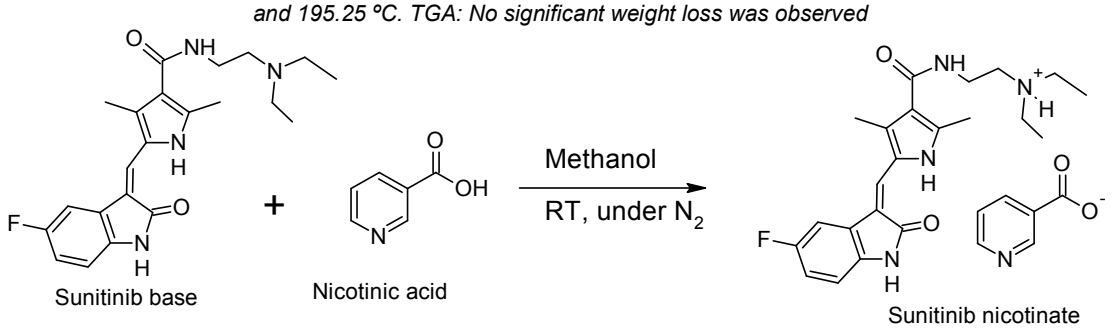


Fig. 4. XRD spectrum of sunitinib 4-hydroxy benzoate

% Yield = 72.8, M. P. = 195.3°C, IR (KBr) V_{max}(in cm^{-1}): 3427, 3190, 3047, 2988, 2207, 1679, 1629, 1572, 1526, 1474, 1441, 1369, 1326, 1280, 1258, 1222, 1195, 1179, 1144, 697, 666 and 589. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (6H, t, C29, 27-H, J = 7.08, 7.12 Hz), 2.43 (6H, d, C18, 21-H, J = 7.64 Hz), 2.49-2.59 (6H, m, C24, 26, 28-H), 32.7-3.32 (2H, m, C23-H), 6.80 -6.86 (3H, m, Ar-H), 6.90-6.95 (1H, m, Ar-H), 7.45 (1H, t, Ar-H, J = 5.48, 5.6 Hz), 7.71-7.79 (4H, m, Ar, 11a, N13-H), 10.8 (1H, s, N22-H), 13.68 (1H, s, N1-H). DSC: Endotherms at 188.22 and 195.25 ºC. TGA: No significant weight loss was observed



Scheme 7. Scheme for the synthesis of sunitinib nicotinate

4. RESULTS AND DISCUSSION

4.1 Z-E Isomerism

HPLC analysis of the lab batches of sunitinib exhibited large variation of the undesired E-isomer content that varied from 0.1% to 8% (Scheme 9). This prompted us to study the probability of the conversion of the sunitinib into the undesired E-isomer in presence of heat and light. This is further confirmed when the solutions, prepared in 1:1 mixture of acetonitrile and water, were exposed to both halogen lamp (20 hours exposure) and sunlight (6 hours) at 10-

15 ºC (during winter). The conversions were found to be about 3% and 28% in halogen lamp and sunlight, respectively (Figs. 7 & 8). This conversion and characterization of E-isomer was additionally supported by ^{1}H NMR spectroscopy. (Conversion Z-isomer 66% and E-Isomer 34%), spectra' s shown in supporting information S1 to S3.

When the samples were kept in dark for about 40 hours, the E-isomer could not be detected in the resulting solutions confirming that the Z-E isomerization in sunitinib is reversible.

4.2 Solid form Screening

Polymorph, co-crystal and salt screening experiments were carried out to identify novel solid forms with the improved physicochemical properties, particularly water solubility in the present case.

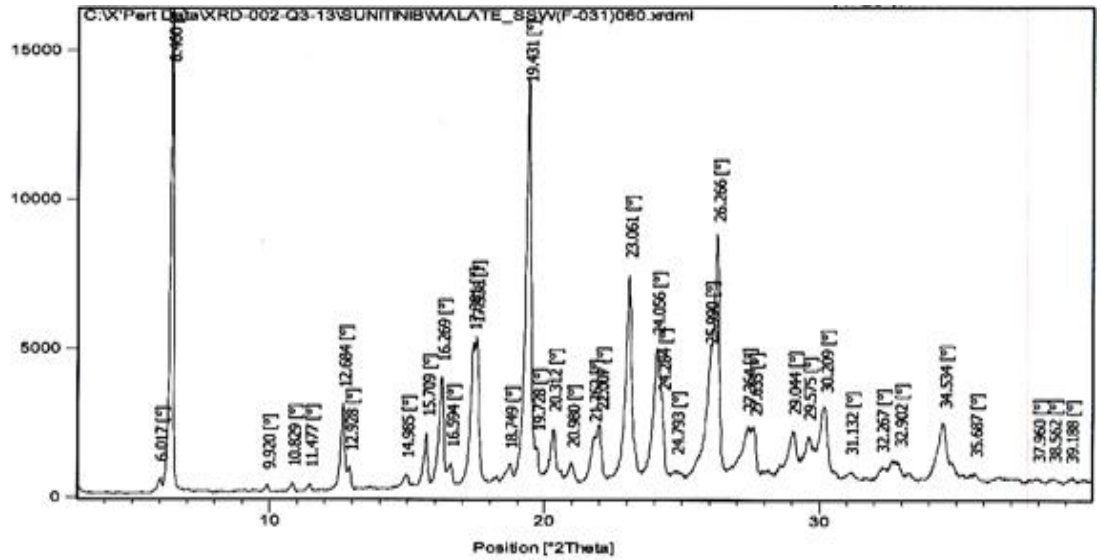
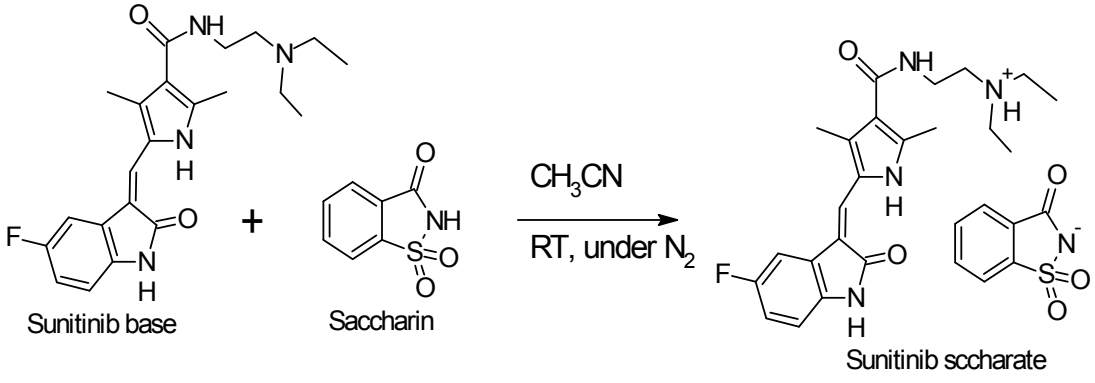


Fig. 5. XRD spectrum of sunitinib nicotinate

% Yield = 60.8, M. P. = 203.3°C, IR (KBr) V_{max}(in cm^{-1}): 3427, 3190, 3047, 2988, 2204, 1679, 1629, 1573, 1526, 1474, 1326, 1195, 1179, 666 and 589. ^{1}H NMR (400 MHz, $CDCl_3$):δ1.03 (6H, t, C29, 27-H, J = 7.12, 7.12 Hz), 2.43 (6H, d, C18, 21-H, J = 7.72 Hz), 2.68 (6H, t, C24, 26, 28-H, J = 7.24, 7.64 Hz), 3.35 (2H, d, C23, J = 6.2 Hz), 6.84 (1H, d, Ar-H, J = 8.44 Hz), 6.92 (1H, t, Ar-H, J = 8.52, 9.48 Hz), 7.48 (1H, dd, Ar-H, J = 4.84, 5.04 Hz), 7.56 (1H, s, Ar-H), 7.75 (1H, d, Ar-H, J =9.4 Hz), 8.21-8.24 (1H, m, Ar-H), 8.72 (1H, dd, Ar-H, J = 1.64, 1.64), 9.04 (1H, t, N22-H, J = 0.76, 1.32 Hz), 10.9 (1H, s, N13-H), 13.68 (1H, s, N1-H), DSC: Single endotherm at 205.25 ºC. TGA: No Significant weight loss



Scheme 8. Scheme for the synthesis of sunitinib saccharate

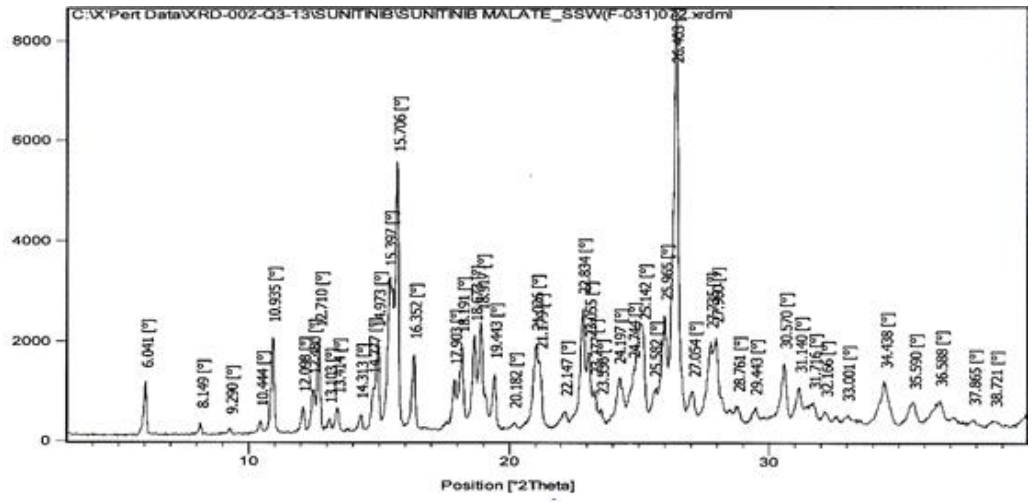
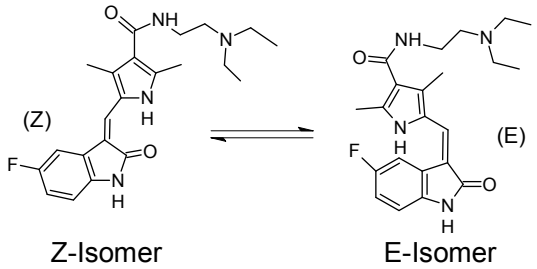


Fig. 6. XRD spectrum of sunitinib saccharate

% Yield = 92.0, M. P. = 202-207°C, IR (KBr) V_{max}(in cm^{-1}): 3429, 3303, 3226, 2969, 2929, 2814, 1824, 1677, 1589, 1542, 1480, 1467, 1333, 1192, 668 and 585. ^{1}H NMR (400 MHz, $CDCl_3$):δ1.24 (6H, t, C39, 41-H, J=7.24, 13.04 Hz), 2.46 (6H, dd, C33, 30-H, J = 11.16, 18.72 Hz), 3.21-3.22 (6H, m, C36, 38, 40-H), 3.58 (2H, t, C35, J = 6.0, 6.04 Hz), 6.86 (1H, dd, Ar-H, J = 4.56, 4.56 Hz), 6.94 (1H, t, Ar-H, J = 8.76, 9.2 Hz), 7.56-7.62 (3H, m, Ar, N1-H), 7.64 -7.67 (1H, m, C23-H), 7.74-7.80 (3H, m, Ar-H), 9.23 (1H, s, N-H), 10.93 (1H, s, N-H), 13.76 (1H, s, N-H), DSC: Single endotherm at 233.07 °C. TGA: No significant weight loss

Polymorph, co-crystal and salt screening experiments were carried out to identify novel solid forms with the improved physicochemical properties, particularly, water solubility in the present case. Three polymorphs of sunitinib malate are reported in the literature.[17-19] Both reactive crystallization and solvent mediated transformation methods were explored in as many as twenty solvents which included EtOH (ethanol), 1-butanol, IPA, ethyl acetate, dichloromethane, DMSO, THF, methyl isobutyl ketone, toluene, heptane, water, 2-methyl THF, acetone, DMF, acetonitrile, cyclohexane and methyl tertiary butyl ether. Only the thermodynamically stable reported form was obtained in the screening experiments. Co-crystal screening experiments were carried out with two coformers, namely, urea and nicotinamide using solvent mediated conversion method in acetonitrile and MeOH. Both these coformers do not have any acidic groups that favor salt formation with sunitinb. The screening results by XRPD revealed that only the physical mixture of components (starting materials) were obtained.

Malate salt of sunitinib is being currently sold in the market. Salt screening experiments were conducted with adipic acid, glutaric acid, nicotinic acid, 4-hydroxy benzoic acid and saccharin as their corresponding salts (Fig. 9) were not covered in the patent literature, and all of them are also well thought-out pharmaceutically acceptable salt formers. The desired salts with 1:1 ratios were obtained when sunitinib was treated with these acids, except for adipic acid, which yielded a 2:1 [sunitinib] [adipic acid] salt. The spectra's of synthesized solid forms shown in supporting information S10 to S29.



Scheme 9. Z-E Isomerization in sunitinib in presence of light

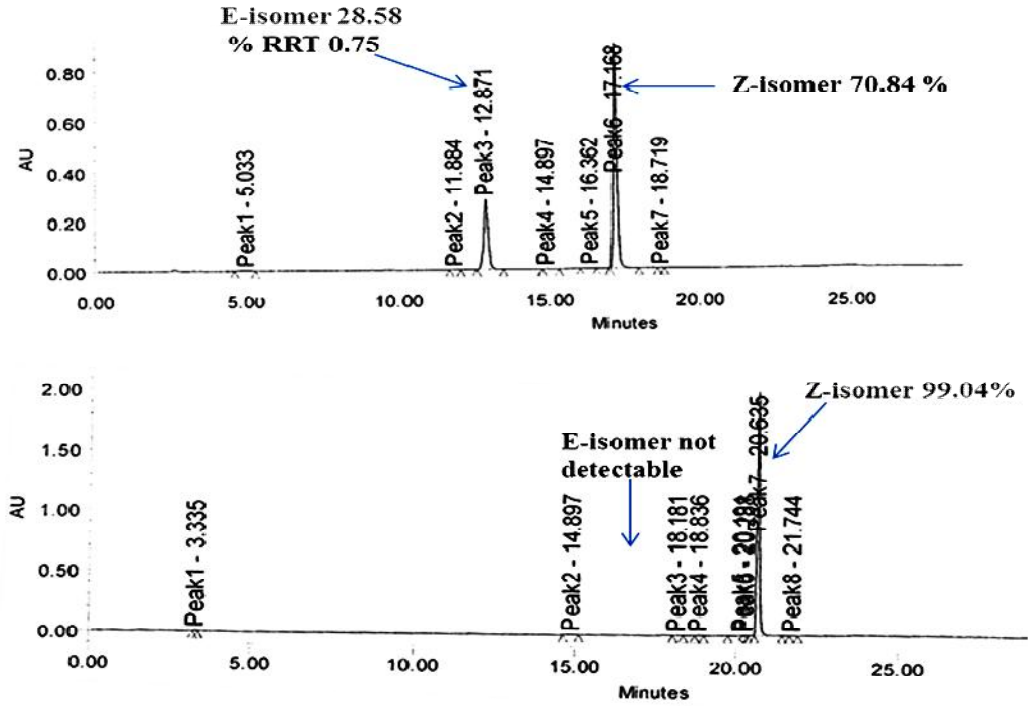


Fig. 7. HPLC chromatogram of the samples exposed to sunlight (above) and then kept in dark (below)

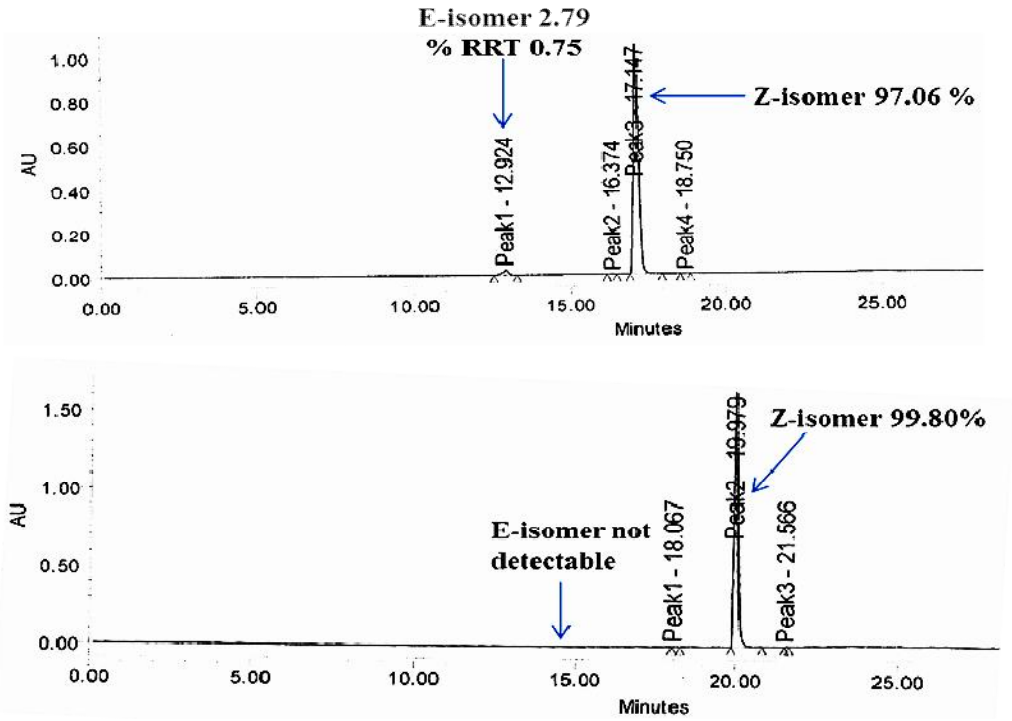


Fig. 8. HPLC chromatogram of the samples exposed to halogen lamp (above) and then kept in dark (below)

The solid form characterization data is shown in Table 1. Glutarate and nicotinate salts show a single endotherm in DSC. TGA data reveals that these salts are neither hydrates nor solvates. The melting points of nicotinate, 4-hydroxy benzoate and saccharate salts are lower than those of the corresponding components (both salt-former and sunitinib), while that of adipate and glutarate salts lie between the melting points the corresponding salt former and sunitinib. Sunitinib base melts at 216.6 ºC with an endotherm in the DSC at 234.4 ºC.

The equilibrium solubility of these solid forms was evaluated by HPLC method. Solubility data revealed that these salts exhibit variable water (DI water) solubility (Table 2). Nicotinate and adipate salts exhibited excellent water solubility, particularly at a higher pH (of about pH 7.0). The solubility of these salts in DI water was found to be 6 to 10 times greater than that of the marketed form (malate salt). Solubility of adipate, glutarate and 4-hydroxy benzoate salts are less soluble in water than the marketed malate salt.

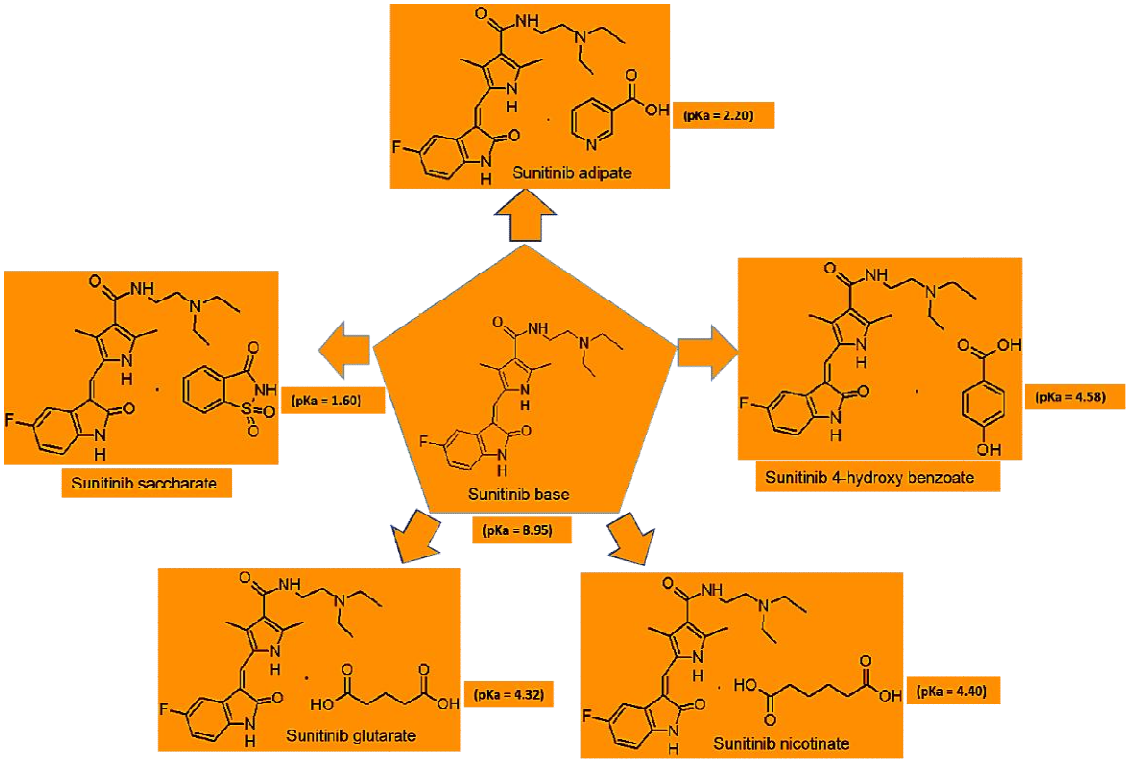


Fig. 9. Adipate, saccharate, 4-hydroxybenzoate, glutarate and nicotinate salts of sunitinib

Table 1. Thermal characterization of various salts identified in the present study

Sunutinib salts	Stoichiometry (base:acid)	Melting point*	DSC*	TGA of salts	Melting point of the salt former
Adipatesalt	1:0.5	200 ºC	184.3, 207.4	No significant weight loss	149-153 ºC
Glutarate salt	1:1	204.2 ºC	202.4	No significant weight loss	94-97 ºC
Nicotinate salt	1:1	203.3 ºC	205.2	No significant weight loss	234-237 ºC
4-Hydroxy benzoate salt	1:1	195.3 ºC	188.2, 195.2	No significant weight loss	214-215 ºC
Saccharate salt	1:1	202-207 ºC	233.1, 222.6	No significant weight loss	225-227 ºC

**Sunitinib base: melting point: 216.6ºC; DSC: endotherm at 234.4ºC*

Another interesting point that is worth noting here is the stoichiometry of the adipate salt. It is likely that both acidic protons of adipic acid are engaged in the protonating sunitinib leading to a 2:1 (sunitinib: adipic acid) salt. Alternatively, the same stoichiometry can be resulted if there one neutral sunitinib, one protonated sunitinib and one singly deprotonated adipic acid species as shown in Fig. 10. If this is indeed the case, then we are in the salt co-crystal region. In other words, the adipate salt referred herein can also be a salt co-crystal. However, this needs to be confirmed by single crystal X-ray diffraction studies.

Table 2. Equilibrium solubility of sunitinib solid forms in DI water at room temperature

Solid form	malate salt	Sunitinib	Adipate salt	Glutarate salt	Nicotinate salt	4-Hydroxy benzoate salt	Saccharate salt
Solubility (mg/ml)	~25 (reported)	~0.048	272	6.2	162	3.42	2

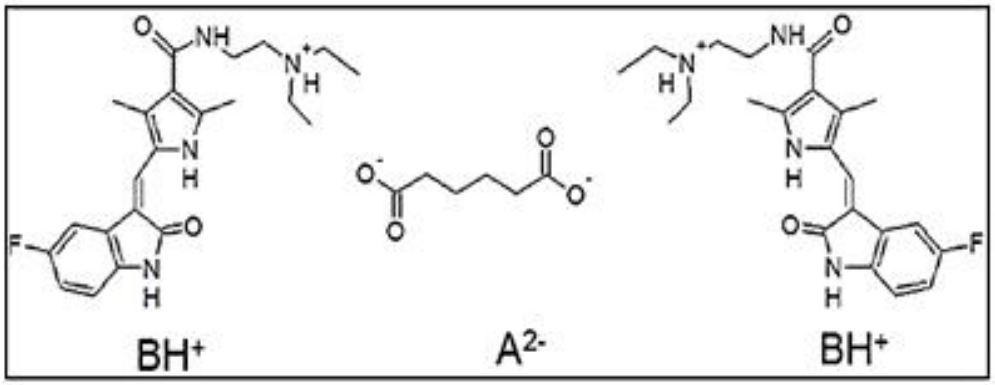


Fig. 10. Two possible solid forms of sunitib with adipic acid for a 2:1 sunitinb: adipic acid stoichiometry: salt (above) / salt co-crystal (below)

Fig. 10. Two possible solid forms of sunitib with adipic acid for a 2:1 sunitinb: adipic acid stoichiometry: salt (above) / salt co-crystal (below)

5. CONCLUSION

Sunitinib base as well as its malate salts are poorly soluble compounds, primarily in water. Consequently novel solid forms of sunitinib were prepared using pharmaceutically acceptable solid form conformers with improved physicochemical properties like solubility. Thermodynamically stable crystalline solid forms of sunitinib adipate, glutarate, nicotinate, 4-hydroxybenzoate and saccharate were prepared by reactive crystallization process, out of which Nicotinate and Adipate salts exhibited excellent water solubility, at a pH of about pH 7.0 in deionized water (DI). The solubility of these salts in DI water was found to be 6 to 10 times greater than that of the marketed form (malate salt). Z-E isomerization in sunitinib was also investigated in presence of light and heat, likewise additionally confirmed by ^{1}H-NMR. Importantly, these results suggest that care should be taken while handling the analytical solutions of this API during HPLC testing for the most part, protection from light and heat for obtaining consistent and accurate data.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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