Ziprasidone malate, a new trimorphic salt with improved aqueous solubility†

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A new salt of ziprasidone with high aqueous solubility has been discovered as a result of a salt screening and it has been found to exist in three anhydrous polymorphic forms. One of these forms shows the highest aqueous solubility ever reported for ziprasidone salts in combination with a high kinetic stability, becoming a good candidate for further pharmaceutical development.

Introduction

Ziprasidone, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl] ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one (Fig. 1) is a poorly soluble drug in water, a factor that unfavorably affects its bioavailability.[1] A problem of major concern is the solubility entailing therapeutic consequences. Ziprasidone, an antipsychotic agent useful for the treatment of psychotic disorders of the schizophrenic types,[2] is marketed under the name GEODON as an oral capsule and as an injectable drug. GEODON capsules contain the monohydrate hydrochloride salt of ziprasidone, whereas GEODON for injection contains ziprasidone mesylate trihydrate. The need for improved water soluble forms of ziprasidone has been recognized during the last years.[1] Dihydrate and trihydrate salts of ziprasidone mesylate have been reported to possess greater hygroscopic stability and greater aqueous solubility than the previously known hydrochloride salts.[3] Ziprasidone hydrogensulfate dihydrate[4] has been recently described with an increased solubility compared with hydrochloride salts. A method has also been reported for improving the solubility of ziprasidone salts by preparing inclusion complexes.[5] There is still the need of developing new soluble salts of ziprasidone suitable for the preparation of pharmaceutical compositions.

Salts are usually employed for increasing aqueous solubility,[6] however the salt form selected can influence many other properties such as melting point, mechanical properties, hygroscopicity, chemical stability, dissolution rate and solution pH.[7]

A salt screening for ziprasidone is presented here. The malate salt has been selected among a variety of salts and it has been found to exist at least in three different anhydrous forms which have been studied and characterized.[8]

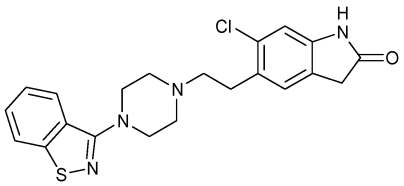

Fig. 1 Ziprasidone.

Results and discussion

Ziprasidone (ZP) is a benzisothiazolyl piperazine compound that exists as a white crystalline solid with a melting point of 226 °C and a very poor aqueous solubility of approximately 0.3 μg mL^{-1}.[9] The pK_a values of the two ionisable groups in the molecule are 8.4 and 13.3. ZP is slightly soluble only in DMF, DMSO, acetonitrile, ethanol, THF and ethyl acetate.[10]

ZP was purified prior to the screening by decoloration in CH_2Cl_2/ethanol using charcoal (10% w/w) at 60 °C for 30 min. During the optimization of this process, single crystals suitable for X-ray structure determination of ZP were grown by chance.[11] The crystal structure is shown in Fig. 2 revealing a hydrogen bonding C–O···H–N zigzag network. Secondary π–π stacking interactions between consecutive planes are also observed.

Salt screening

It is commonly accepted that the formation of a stable salt requires a difference of at least 3 units between the pK_a value of the ionisable group and that of the counterion.[12] So, we selected a range of acids according to this information: phosphoric, citric, lactic, malic, gluconic, maleic, fumaric, glutaric, oxalic, glutamic,

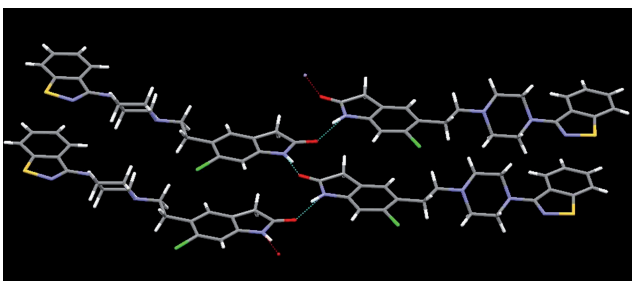

Fig. 2 Single crystal X-ray structure of ziprasidone.

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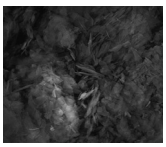
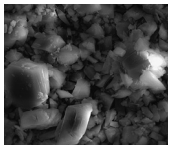
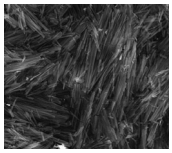
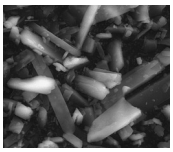
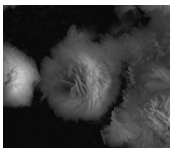
Table 1 Ziprasidone salts obtained during the screening

Salt	Phosphate	Citrate	Fumarate	Oxalate	Malate	Isethionate
Solvent	THF	THF	EtOAc	THF	EtOAc	THF
Stoichiometry	1 : 1	1 : 1	2 : 1	1 : 1	1 : 1	1 : 1
DSC (mp, °C)	243	216	204	247	198	236
Other thermal behaviour	—	—	Crystallization from the melt	—	Endothermic solid transition	—
PXRD	Crystalline	Crystalline	Crystalline	Crystalline	Crystalline form A	Crystalline
Physical appearance						

2-hydroxyethanesulfonic (isethionic) and naphthalene-1,5-disulfonic acids.

Initially, a microscale screening in different solvents allowed us to discard lactic, gluconic, glutaric, maleic, glutamic and naphtalene-1,5-disulfonic acids from the selected list before completion of the study because no salt was isolated from these acids. Moreover, this previous study helped us to identify the most suitable combinations of solvent and counterion.

Next, a screening at a larger scale was developed with the remaining acids. The obtained salts were characterized by DSC, PXRD, IR and ^{1}H-NMR. In Table 1 the most relevant data are summarized.

Additionally, the aqueous solubility of these salts was determined in order to compare the data obtained with the previously known solubilities of hydrochloride and mesylate salts. The aqueous solubilities have been determined by means of HPLC with UV detection (λ = 229 nm). The method is based on the comparison between saturated solutions of each salt in water at room temperature with ZP standards.[5] Quantification can be effected by comparison of HPLC peak area with the peak area taken from a standard plot of concentration *vs.* peak area for standards of known concentrations. Using the above procedure the obtained ziprasidone salts were tested. The results are reported in Table 2.

Phosphate, citrate and fumarate were initially discarded because their solubilities (<100 μg mL^{-1}) are very poor. As can be seen, the isethionate salt is the one with the highest solubility. However, the appearance of colored impurities during its isolation together with the poor recovery forced us to reject this salt.

Table 2 Aqueous solubilities of ZP salts by HPLC at 25 °C

Salt	Aqueous solubility[a]/μg mL^{-1}
Free base	0.3[5]
Hydrochloride	80[5]
Mesylate	1000[5]
Phosphate	28
Citrate	30
Fumarate	55
Oxalate	236
Isethionate	1121
Malate	475

[a] Solubility values indicate the weight in μg of ziprasidone calculated as the free base, per mL of water.

Then, our efforts were directed towards the malate salt as the selected target for further studies due to its good solubility. Moreover, malic acid is generally regarded as safe (GRAS) by the FDA and has previously been used in FDA-approved marketed drugs.[13]

The malate salt of ZP

During the salt screening, evidence of the polymorphic behavior of the malate salt of ZP was observed. Therefore, we decided to explore more deeply this salt by conducting a polymorph screening of this compound. Using a broad set of thermodynamic and kinetic crystallization conditions, we were able to isolate three different anhydrous crystalline forms.

Forms A and B were obtained by slurring ZP at 60 °C in ethyl acetate or acetonitrile, respectively, and adding an equimolar amount of malic acid, whereas form C was isolated from a suspension of ZP in acetonitrile at room temperature after the addition of an equimolar amount of malic acid (Fig. 3).

Each form was characterized by means of DSC, PXRD, IR and ^{1}H-NMR spectroscopy. Fig. 4 shows the X-ray diffraction patterns revealing significant differences, while IR spectra are very similar (data not shown).

DSC thermograms of the different ZP malate forms are shown in Fig. 5. As can be seen, form A shows an endothermic

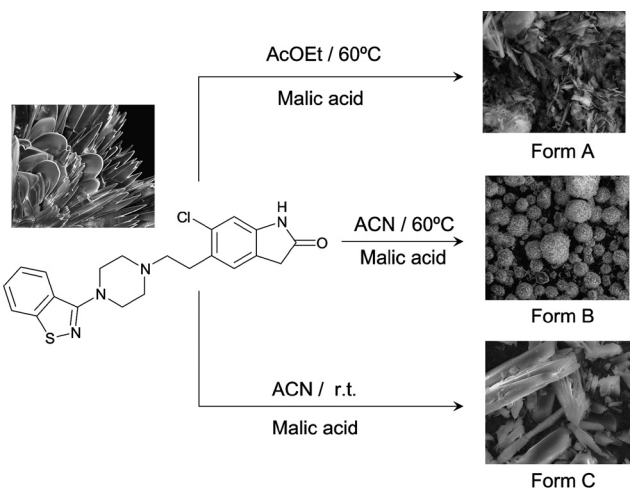


Fig. 3 Crystallisation of the polymorphs of the malate salts of ZP.

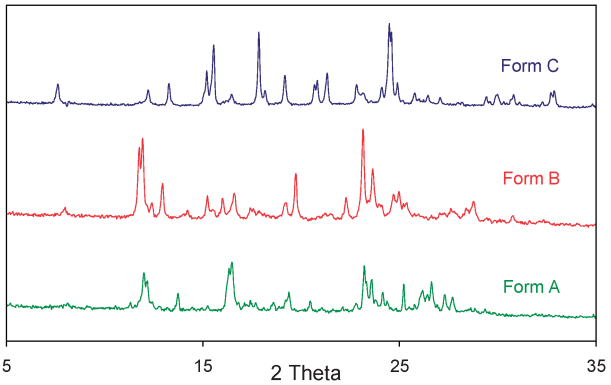


Fig. 4 PXRD of forms A, B and C of ZP malate.

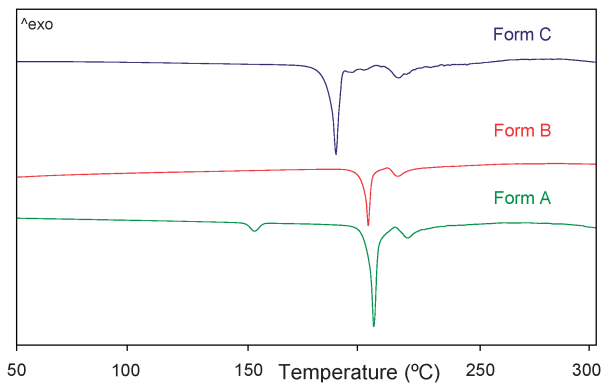


Fig. 5 DSC of forms A, B and C of ZP malate.

solid–solid transition at 149 °C towards a higher melting form, which melts at 198 °C. After this melting, an endothermic phenomenon is observed which corresponds to the release of a COOH fragment, confirmed by thermogravimetric analysis. Form B melts at 197 °C and form C at 181 °C, both also followed by the same decarboxylation.

Once the three different forms of ZP malate were isolated, their aqueous solubilities were evaluated (Table 3). Interestingly, forms B and C show an improved high solubility value of 989 and 1084 μg mL^{-1}, respectively, as compared to the malate form A. In addition, these solubility values are in the same range as that of mesylate.

In this sense, malate salts of ZP seem to be good candidates for further pharmaceutical development. However, it is of great relevance, and even a regulatory requirement, to know whether polymorphic modifications can transform reversibly (enantiotropy) or irreversibly (monotropy) at atmospheric pressure.[14]

Table 3 Aqueous solubilities of the malate salts of ZP by HPLC

Salt	Aqueous solubility[a]/μg mL^{-1}
Malate form A	475
Malate form B	989
Malate form C	1084

[a] Solubility values indicate the weight in μg of ziprasidone calculated as the free base, per mL of water.

When a compound exhibits polymorphism of an enantiotropic type, the knowledge of the different domains of thermodynamic stability for each form is crucial in order to obtain the desired form through a robust crystallization process and to define the appropriate storage conditions.[15]

The relative thermodynamic stability between each pair of polymorphs has been studied. Form A shows an endothermic solid–solid transition followed by the melting of form B. Then, according to the "heat of transition rule" of Burger and Ramberger,[16] A and B are enantiotropically related, A being more stable than B from room temperature to the transition temperature. On the other hand, the determination of the thermodynamic relationship between B/C forms is based on the fact that polymorph B is the one with the highest melting point and the lowest solubility (highest stability)[17] at room temperature, then B/C are monotropically related, B being more stable than C at any temperature. Finally, the thermodynamic relationship between A/C forms cannot be fully determined because the melting of form A has never been observed in a DSC experiment, even at high heating rates. Taking into account that A is less soluble (*i.e.* more stable) than C at room temperature and that B and C are monotropically related (B being more stable than C), then A must be more stable than C at least until the transition temperature between A/B forms (tr A → B). Therefore, A/C forms can be either monotropically or enantiotropically related after tr A → B. All this information is summarized in the energy *vs.* temperature diagram (Fig. 6).

Commonly, the most stable polymorphic modification is used in a marketed formulation, because any other polymorphs are metastable and may therefore transform into the most stable form. Overlooking the most stable polymorph may cause failure of a marketed product because a phase transformation during storage can occur. A late-appearing stable polymorph can have a great impact on development timelines.[18] However, metastable forms may survive years if a high activation energy barrier has to be overcome in moving from the metastable form to the stable one. In the present case, the three anhydrous forms of ZP malate have shown to be stable after three months of storage at room temperature and 60% of relative humidity (RH) and two weeks at 75% RH (by using NaCl saturated solution to control the RH level in a sealed dessicator).

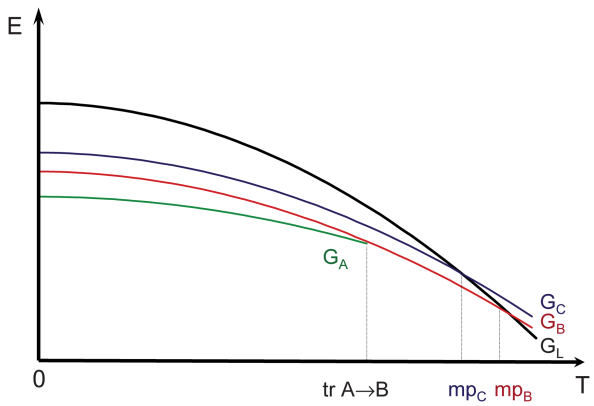


Fig. 6 Energy/temperature diagram of the three anhydrous ZP malate forms.

Experimental

Material

A sample of ZP was provided by Laboratorios Lesvi and was purified by decoloration in CH_2Cl_2/ethanol using charcoal (10% w/w) at 60 °C for 30 min.

X-Ray powder diffraction

X-Ray powder diffraction patterns were obtained on a Debye-Scherrer INEL CPS-120 diffractometer, equipped with a Cu Kα source (λ = 1.54056 Å) and a 120° curved position sensitive detector, operating at 40 kV and 30 mA. Each sample was scanned between 0 and 115° in 2θ, with a step size of 0.029° and a scan rate of 3600 s step^{-1}.

Single crystal X-ray diffraction

A prismatic crystal (0.1 × 0.1 × 0.2 mm) was selected and mounted on a Enraf-Nonius CAD4 four-circle diffractometer. Unit-cell parameters were determined from automatic centering of 25 reflections ($12 < \theta < 21°$) and refined by the least-squares method. Intensities were collected with graphite monochromated Mo Kα radiation, using a $\omega/2\theta$ scan-technique. 5855 reflections were measured in the range $2.61 \leq \theta \leq 30.14$, 5773 of which were non-equivalent by symmetry (Rint(on I) = 0.052). 3136 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarization but no absorption corrections was performed.

The structure was solved by direct methods, using the SHELXS computer program (Sheldrick, G.M., (1997), a program for automatic solution of crystal structure refinement, Univer Goettingen, Germany) and refined by full-matrix least-squares method with SHELX97 computer program (Sheldrick, G.M., (1997), A program for crystal structure refinement, Univer Goettingen, Germany), using 5855 reflections, (very negative intensities were not assumed). The function minimized was $\sum w||Fo|^2 - |Fc|^2|^2$, where $w = [\sigma 2(I) + (0.1192P)^2 + 0.6288P]^{-1}$, and $P = (|Fo|^2 + 2|Fc|^2)/3$, f, f' and f'' were taken from International Tables of X-Ray Crystallography (International Tables of X-Ray Crystallography, Kynoch press, Vol. IV, 1974, pp 99–100 and 149). All H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor. The final R(on F) factor was 0.068, wR(on $|F|2$) = 0.229 and goodness of fit = 1.034 for all observed reflections. Number of refined parameters was 337. Max. shift/esd = 0.00, Mean shift/esd = 0.00. Max. and min. peaks in final difference synthesis were 0.589 and −0.330 e Å^{-3}, respectively.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminum crucibles of 40 µL volume, atmosphere of dry nitrogen with 50 mL min^{-1} flow rate, heating rate of 10 °C min^{-1}. The calorimeter was calibrated with indium of 99.99% purity.

Thermogravimetric analysis (TGA)

Thermogravimetric analyses were performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 µL volume, atmosphere of dry nitrogen with 50 mL min^{-1} flow rate, heating rate of 10 °C min^{-1}.

FT-IR

FT-IR spectra were recorded on a Bomem MB-120 IR spectrophotometer in KBr pellets, at 1 cm^{-1} resolution, from 350 to 5000 cm^{-1}.

SEM

Scanning electron microscopy was recorded on a ESEM Quanta 200 microscope from FEI with a LFD detector, using 20 KV.

Salt screening experiments

The microscale previous screening was performed as follows: 50 mg of ZP were suspended in 5 mL of each selected solvent and the mixture was heated at 60 °C for 1 h. Then an equimolar amount of each acid was added and the mixture was stirred for 2 h at 60 °C and for 12 h at room temperature. The obtained solid was filtered, washed and analyzed by DSC, PXRD and ^{1}H-NMR. The larger scale screening was performed in the same manner by using 400 mg of ZP and 40 mL of the selected solvent.

Solubility determination by HPLC

The solubility of ZP salts was determined by an HPLC method which calculates ziprasidone concentration as free base. In this method an excess amount of the tested salts is stirred between 45 min to 1 h at 25 °C in water and the saturated solutions are filtered and analyzed[19] through an HPLC method to determine the concentration of the salt dissolved, which corresponds to the solubility of the salt in water. The concentration of ZP is determined by using a YMC Pack Pro C185 50 µm × 4.6 mm column with a mobile phase consisting of H_2O-MQ + 0.1% formic acid and acetonitrile + 0.1% formic acid with a variable gradient, at a flow rate of 1.00 mL min^{-1} at 40 °C. Detection can be made by UV absorption at a wavelength of 229 nm. Quantification can be effected by comparison of HPLC peak area with the peak area taken from a standard plot of concentration *vs.* peak area for standards of known concentration. As is conventional, the ziprasidone standard concentrations are selected to fall within a linear range of concentration *vs.* absorbance for the UV detector employed. The saturated equilibrium solution obtained after filtering the vial test solution may need to be diluted in serial fashion to reach the linear range of the standard plot, and dilution can be effected by adding water.

Preparation of the malate salt of ZP Form A

Ziprasidone (100 mg, 0.24 mmol) was suspended in 10 mL of ethyl acetate. The suspension was then stirred at 60 °C for 1 h and 33 mg (0.25 mmol) of malic acid were added. After 2 h of stirring at 60 °C, the heating was stopped and the suspension was stirred overnight at room temperature (20–25 °C). The resulting solid was recovered by filtration, washed with acetone and dried

under vacuum at room temperature (20–25 °C). 130 mg (98%) of the malate salt of ziprasidone Form A were obtained.

Preparation of the malate salt of ZP Form B

Ziprasidone (1.0 g, 2.4 mmol) was suspended in 100 mL of acetonitrile. The suspension was then stirred at 60 °C for 30 min and 0.324 g (2.4 mmol) of malic acid were added. After 2 h of stirring at 60 °C, the heating was stopped and the suspension was stirred overnight at room temperature (20–25 °C). The resulting solid was recovered by filtration, washed with acetone and dried under vacuum at room temperature (20–25 °C). 1.25 g (95%) of the malate salt of ziprasidone Form B were obtained.

Preparation of the malate salt of ZP Form C

Ziprasidone (7.0 g, 17 mmol) was suspended in 700 mL of acetonitrile. The suspension was then stirred at room temperature (20–25 °C) for 30 min and 2.4 g (17 mmol) of malic acid were added. After 2 h of stirring at room temperature (20–25 °C), the resulting solid was recovered by filtration, washed with acetone (2 × 10 mL) and dried under vacuum at room temperature (20–25 °C). 8.8 g (95%) of the malate salt of ziprasidone form C were obtained.

Conclusions

In this study we have conducted a salt screening of ZP with twelve of the most common acids and the aqueous solubility of those that yielded salts, has been measured. The malate salt was selected for further investigation due to its high solubility and this salt turned out to be polymorphic with at least three crystal anhydrous modifications. These forms have been fully characterized. Form C shows the highest aqueous solubility ever reported for ZP salts (14-fold better than the marketed ziprasidone hydrochloride salt, GEODON capsules) in combination with a high kinetic stability, becoming a good candidate for further pharmaceutical development.

Acknowledgements

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10 Prior to the salt screening, a solubility study of ZP was performed with 21 common solvents of different properties. ZP was soluble (10 mg mL^{-1}) in DMF at 50 °C and in DMSO at 70 °C. ZP was soluble (5 mg mL^{-1}) in THF at 50 °C. ZP was partially soluble (< 3 mg mL^{-1}) in ethanol, acetonitrile, dioxane and ethyl acetate at 70 °C. ZP was not soluble (< 1 mg mL^{-1}) in methanol, isopropanol, *tert*-butanol, diethylether, methylethylketone, acetone, methylisobutylketone, water, toluene, pentane, cyclohexane, heptane, dichloromethane, xylene and ethyleneglycol. The screenings were performed using the following selected solvents: DMSO, DMF, THF, ethanol, ethyl acetate, acetonitrile, isopropanol and water.
11 Crystal data for ZP: crystal dimensions: 0.19 × 0.18 × 0.09 mm^3; monoclinic $P2_1/a$, a = 7.377(8), b = 8.038(3), c = 33.627(6) Å, β = 95.60(4)°, V = 1984(2) $Å^3$, Z = 4, ρ_{calcd} = 1.382 g cm^{-3}, R_{int} = 0.0524, $R1$ = 0.0677, $wR2$ = 0.1722 Final R indices [$I > 2\sigma(I)$]. CCDC 694162.
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19 We report solubilities after stirring saturated salts between 45 min to 1 h because we have observed that malate salts transform into the hydrated form (which is less soluble) when they are stirred in water for 30 h.