Drug Development and Industrial Pharmacy, 2011; 37(6): 719–726

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.538060

informa
healthcare

RESEARCH ARTICLE

Early development evaluation of AZD2738, a substrate for the NK receptors

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Abstract

The purpose of this study was to investigate whether AZD2738, a dual neurokinin NK1/2 receptor antagonist, is a suitable candidate for further development with an oral immediate release solid dosage form as a possible final product. The neutral form of AZD2738 has only been isolated as amorphous material. In order to search for a solid material with improved physical and chemical stability and more suitable solid-state properties, a salt screen was performed. Mostly crystalline material of fumarate, maleate and chloride salt of AZD2738 were obtained. X-ray powder diffractometry, thermogravimetric analysis, differential scanning calorimetry and dynamic vapor sorption were used to investigate the physicochemical characteristics of the salts. Based on the physicochemical properties, the chloride salt is preferred for continued product development. The chloride salt of AZD2738 is an anhydrate, the crystallization is reproducible, the hygroscopicity is acceptable and just one polymorph was obtained. Notably is that the two obtained polymorphs of the fumarate salt of AZD2738 are monotropically related, whereas the two identified polymorphs for the maleate salt of the compound are enantiotropic. The dissolution behavior and the stability (in aqueous solutions, formulations and solid state) of the salts were also studied and found to be satisfactory, at least at pH >3. Liquid formulations should preferable be stored frozen at pH >3.

Keywords: NK receptor, preformulation, salt screen, solid state, stability

Introduction

Three major receptors for tachykinins have been identified, the neurokinin (NK) 1, 2 and 3 receptors[1,2]. A wide distribution of NK1 receptors has been shown. The receptors are mainly located close to sensory neurons in the brain, but to some degree these are present in the gut as well.[3]. NK2 receptors are primarily detected in the periphery and its expression in the central nervous system (CNS) appears to be minor[4–9]. NK3 receptors are mainly expressed in the CNS and have only been detected in certain peripheral tissues[5,10–14].

AZD2738 (Figure 1) binds to at least these three NK receptors with different dignity, but preferably to receptors 1 and 2, and is developed to be a possible treatment within IBS (irritable bowel disease).

Before product development, it is essential that certain fundamental physical and chemical properties of the drug molecule are determined. This information dictates many of the subsequent events and approaches in the formulation development. This first learning phase is known as preformulation or early development. These early studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form development. One of the first steps in preformulation is to establish simple analytical methods to be able to measure solubility and follow stability of the substance. It is of high importance to identify any instability in pharmaceutical formulations as early as possible in the development process[15]. It is also important to investigate, and in some cases, improve, the solid-state properties of the substance to find a suitable, preferable crystalline material, for further development. For example, solubility, dissolution rate, stability and physical form can be modified by selection of different salt forms. The process of

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(Received 16 June 2010; revised 22 October 2010; accepted 03 November 2010)

selecting an appropriate salt is therefore an essential part of the preformulation stage of drug development.

Identifying and characterizing different crystal forms (polymorphs, as well as solvates, of the neutral form or a selected salt) of a drug is the next step in solid-state characterization[16,17]. Different crystal modifications may lead to differences in solubility and dissolution rate[18–20], morphology and color[21], mechanical properties[22,23] and physicochemical stability [24]. During early development, it is well motivated to initiate such a solid-state evaluation. In addition, patenting new solid forms is an important part of modern life-cycle management of innovative pharmaceutical compounds[25].

The purpose of this study was to investigate whether AZD2738 is a suitable candidate for further development with an oral immediate release (IR) solid dosage form as a possible final product. In the present work, we have used a salt screen approach to identify a suitable test compound for further product development. An initial slurry study was performed to get an idea of the tendency of the present salts to adopt alternative crystal modifications. Chemical and physical stability testing of the identified salts of AZD2738 were investigated under various temperature and humidity as well as in different liquid solutions.

Materials and methods

The test compound

AZD2738 (Figure 1) was obtained from AstraZeneca (Mölndal, Sweden) and Albireo Pharma (Göteborg, Sweden). The substance (628.5 g/mol) is a base with pK_as of 3.1 and 8.6 (determined by capillary electrophoresis). Estimated log D at pH 6.8 (from k′ = 10.8, obtained by liquid chromatography–mass spectrometry) is 2.9.

Chemicals

Acetonitrile, methanol, n-heptane, trifluoroacetic acid (TFA) and acetone were bought from Merck (Darmstadt, Germany). Chloroform was obtained from Sigma Chemicals (St Louis, MO), whereas tetrahydrofuran (THF) and 2-propanol were from Rathburn Chemicals (Walkerburn, Scotland). Ethyl methyl ketone (EMK), methyl isobutyl ketone (MIBK) and ethylacetate were from Scharlau Chemie (Sentmenat, Spain) and ethanol was bought from Kemetyl (Haninge, Sweden). Isooctane and mannitol were bought from Riedel-de Haën (Sigma-Aldrich Laborchemikalien, Seelze, Germany). All counter-ions used in the salt screen (see below) were purchased from Sigma-Aldrich (Steinheim, Germany).

X-ray powder diffractometry

X-ray powder diffractometry (XRPD) experiments were performed on a D8 Advance diffractometer (Bruxer AXS GmbH, Karlsruhe, Germany) with Bragg-Brentano geometry, equipped with a VÅNTEC-1 position sensitive detector. Nickel-filtered Cu K_α radiation was used.

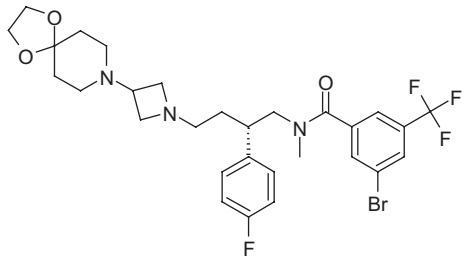

Figure 1. The structure of AZD2738.

The samples, ~10 mg, were mounted on a zero-background holder (silicon crystal). Data were collected using continuous scan mode in the range 1–50° 2θ, with a step size of 0.017° and a step time of 0.5 s. A variable (V20) divergence slit and a detector slit of 12 mm, corresponding to a 3.47° wide detector window, were applied.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) analysis was performed using a DSC Q1000 (TA Instruments, New Castle, DE). The temperature and heat flow were calibrated using indium. Experiments were run between 25–200 or 250°C with a heating rate of 10°C/min in a dry purge of nitrogen gas (50 ml/min). The sample was analyzed in an aluminium pan with closed lid; however, an ~1-mm wide hole had been made in the lid with a needle.

Thermogravimetrical analysis

Thermogravimetrical analysis (TGA) was performed using a TGA Q500 (TA Instruments, New Castle, DE). The temperature was calibrated using the Curie points of alumel alloy and nickel. The balance was calibrated using 100 and 1000 mg standard weights. The samples were heated from room temperature to 220°C with a heating rate of 10°C/min in a dry purge of nitrogen gas (90 ml/min).

Dynamic vapor sorption

Water sorption measurements were carried out using a commercial instrument: dynamic vapor sorption, DVS-1; Scientific & Medical Products Ltd, Manchester, UK. The automated instrument measures the uptake or loss of water vapor gravimetrically using a Cahn D200 recording ultra-microbalance, in a symmetric arrangement of sample and reference weighing pan, with a mass resolution of 0.1 μg. The relative humidity (RH) around the sample is controlled by mixing saturated (100% RH) and dry (0% RH) nitrogen carrier gas streams to a target RH using electronic mass flow controllers. In addition, the target RH and temperature are measured/verified with solid-state transducers near the sample and reference pan. The whole system is enclosed in a research incubator maintaining constant temperature to within 0.1°C. The target RH and the RH transducers were calibrated/checked to be within 0.05% RH units by measuring the RH in equilibrium with saturated aqueous salt solutions

(NaCl, LiCl and $MgCl_2$) and comparing with literature RH values.

The water sorption isotherm of a sample (typically 5–30 mg) was obtained using a predetermined analysis program (time vs. % RH) which exposed the sample to a constant % RH for sufficiently long time to allow equilibrium sorption to be attained, and thereafter the % RH was changed in order to determine a next equilibrium allowing a complete sorption/desorption curve (e.g. % weight increase vs. % RH and time) to be obtained in one extended run (typically 24 h). Usually the sample was subjected to two consecutive sorption/desorption cycles.

Salt screen

Salt screening was carried out in small scale (1 mg of AZD2738 per experiment) using 30 pharmaceutically relevant counter-ions[26–28]. The solvents were evaporated under a gentle nitrogen purge on a shaking table. The obtained solids were examined for crystallinity by microscopy using an Olympus microscope and crossed polarizer (Olympus IX71; Olympus Optical Co., Ltd, Japan). The crystalline samples were then analyzed for proof of salt formation using Raman microscopy (Labram HR 800 Raman microscope; Jobin Yvon/Horiba, Edison, NJ). Re-crystallizations were attempted in similar conditions from methanol, ethanol, ethylacetate and acetonitrile.

Slurries

The samples (about 40 mg) were suspended in about 500 µl of water, ethanol, methanol, 2-propanol, isooctane, n-heptane, ethylacetate, acetone, acetonitrile, chloroform, THF, EMK or MIBK. They were stored at room temperature for 2 weeks. Small amount of samples of suspension were withdrawn at suitable time intervals and dried at room temperature.

Analytical equipment

A high-performance liquid chromatography system, Agilent 1100 system (Agilent, Waldbronn, Germany) equipped with a diode array detector was used for the analysis of organic impurities in the substance and for the concentration analysis.

The mobile phases consisted of 0.025% volume TFA in water and in acetonitrile. The analysis was performed as a gradient method from 10 to 100% acetonitrile with 0.025% (volume) TFA. Detection was performed with one wavelength at 220 nm.

Liquid chromatography method for purity measurements

The liquid chromatography (LC) column used was a Supelcosil LC-ABZ+Plus with the dimensions 250 × 4.6 mm with 5 µm silica particles (Supelco, Bellefonte, PA). The samples were prepared to a concentration of ~0.3 mg/ml by dissolving the substance in 10% acetonitrile in water.

The counter-ion to the substance, that is maleate and fumarate eluated as a broad peak early in the chromatogram but did not interfere with the peak of the substance and the organic impurities. The resolution between the main peak and the two peaks surrounding the main peak was 3.31 and 3.72. The repeatability of the method was expressed as peak area and retention time, 0.07 and 0.35% (RSD%, $n = 6$).

LC method for measuring the concentration of AZD2738

The LC column used was a Sunfire C18 with the dimensions 100 × 4.6 mm with 3.5 µm silica particles (Waters, Milford, MA). The samples were diluted to a concentration of ~200 µM with 10% acetonitrile in water.

The counter-ion to the substance, that is maleate and fumarate eluated as a peak early in the chromatogram and did not interfere with the peak of the substance.

The repeatability of the method was 0.12% (RSD%, $n = 6$). Linearity was tested between 14 and 272 µM and a correlation coefficient (r^2) of >0.99 was obtained.

Results and discussion

Solubility and stability in solutions for the amorphous neutral form of AZD2738

The neutral form of AZD2738 has only been obtained in amorphous form with a glass transition temperature (T_g) below room temperature. This material is sticky and very difficult to handle. The solubility of AZD2738 is exponentially dependent on the solution pH below the pK_a values (3.1 and 8.6). The solubility in water, at room temperature, using the amorphous neutral form, is >200 mM (pH 6).

For stability studies of formulations, 2, 20 and 200 mM formulations of AZD2738 were manufactured, using a 5% mannitol solution with equimolar amounts of HCl (i.e. 1:1 substance:HCl, pH >5). Samples of each formulation were stored in refrigerator (8°C), in freezer (–20°C) and at room temperature (22°C) for 1 month. The analytical results are given in Table 1. The substance was stable during all conditions.

In an extension of the stability studies, a stability study with buffered aqueous solutions was performed.

Table 1 . AZD2738 (amorphous neutral compound) in water with 5% mannitol and equimolar amounts HCl, pH 5.9 (200 mM), pH 6.6 (20 mM) and pH 6.7 (2 mM).

	Day 0	Day 7/14	Day 30
2 mM, 22°C	95.7	95.4/95.2	95.3
2 mM, 8°C	95.7	95.7/95.5	95.6
2 mM, –20°C	95.7	95.6/95.6	95.5
20 mM, 22°C	95.5	95.6/95.6	ND
20 mM, 8°C	95.5	95.6/95.7	95.7
20 mM, –20°C	95.5	95.5/95.7	95.6
200 mM, 22°C	95.5	95.4/95.4	95.3
200 mM, 8°C	95.5	95.6/95.6	95.6
200 mM, –20°C	95.5	95.5/95.7	95.6

Listed as % remaining in LC purity.
ND, not determined.

The solution stability at different pH values ranging from pH 1 to 7 (the physiologically relevant range) was investigated (Table 2). The neutral form was stable in solution for at least 1 week, at neutral pH. In the solution with the lowest pH value (pH 1, see also Tables 7–9) a small degradation was observed. Two peaks increased in the chromatogram, at 17.2 and 17.4 min (the main peak eluated after 17.8 min). The former was the degradation product where the para-fluoro was lost and the latter peak derived from an unknown degradation product.

Table 2 . Stability in solution of AZD2738 at room temperature with a concentration of 20 mM.

Conditions	pH 1	pH 3	pH 5	pH 7
Day 0 (%)	96.4	96.4	96.5	96.6
Day 7 (%)	94.9	95.7	96.8	96.9
pH of buffer before the substance was added	1.05	3.14	5.01	7.00
pH of solution when the substance was added	1.21	5.46[a]	5.32	7.20

Listed as % remaining in LC purity. Four different solutions, 0.1 M HCl with pH 1, 0.1 M phosphate buffer with pH 3, 0.1 M acetate buffer with pH 5 and 0.1 M phosphate buffer with pH 7, were used.
[a]The reason for the change of pH is unknown.

In vivo formulations of the amorphous neutral form of AZD2738

The neutral form of the substance was used in *in vivo* studies and the exposure was dose linear up to at least 50 μmol/kg in dog and 200 μmol/kg in rat (data not shown). In these experiments, formulations were used in which equimolar amounts of HCl were added to an aqueous solution of AZD2738 with 5% mannitol (w/w) present. Mannitol was included as a tonicity modifier in order to be able to use the same formulation for iv administration. Studies with NaCl as tonicity modifier were also performed as well as oral administration of just pH-adjusted aqueous solutions (data not shown).

In some future iv studies, filtration may be a step in formulation manufacturing. The possibility to filtrate the neutral form of AZD2738 was investigated. 19 mM of the substance was filtrated (the volume used was 500 μl), using a 0.22-μm filter. The initial concentration remained after the filtration step. Similar experiments were performed at 5 mM. No significant amounts of the substance were lost.

For safety assessment and early phase I clinical studies, vehicles will be required that can deliver high doses of test compound for oral as well as iv administration. This can obviously be achieved by using pH-shifted aqueous

Table 3. Solid-state properties of the salts of AZD2738.

Sample	XRPD	DSC	TGA	DVS
AZD2738 fumarate	Mostly crystalline, polymorphic	191°C and 195°C, respectively	(25–190°C): 0.2% (w/w)	0.9% (w/w) from 0% RH to 80% RH
AZ1D2738 maleate	Crystalline	145°C	(25–140°C): 0.1% (w/w)	0.7% (w/w) from 0% RH to 80% RH
AZ1D2738 chloride	Crystalline	196°C	(25–110°C): 0.1% (w/w)	0.9% (w/w) from 0% RH to 80% RH

Table 4. Solid-state chemical stability of AZD2738 fumarate at 25°C/60% RH and 40°C/75% RH (open container) and 80°C.

Conditions	Day 0	Day 3	1 week	2 weeks	1 month	2 months	3 months
25°C/60% RH (closed container)	96.5	96.5	96.3	96.2	96.3	96.4	96.2
40°C/75% RH (open container)	96.5	96.5	96.4	96.3	96.4	96.4	96.4
80°C (closed container)	96.5	96.7	96.5	96.4	96.4	96.3	96.4

Listed as % remaining in LC purity. Note that closed container means that the substance was not exposed to RH, even if the vial was placed in that climate.

Table 5. Solid-state chemical stability of AZD2738 chloride at 25°C/60% RH and 40°C/75% RH (open container) and 80°C.

Conditions	Day 0	Day 3	1 week	2 weeks	1 month	2 months	3 months
25°C/60% RH (closed container)	97.2	97.2	97.4	97.0	97.3	97.2	97.3
40°C/75% RH (open container)	97.2	97.3	97.3	97.3	97.3	97.4	97.3
80°C (closed container)	97.2	97.3	97.1	97.2	97.3	97.5	97.3

Listed as % remaining in LC purity. Note that closed container means that the substance was not exposed to RH, even if the vial was placed in that climate.

Table 6 . Solid-state chemical stability of AZD2738 maleate at 25°C/60%RH and 40°C/75%RH (open container) and 80°C.

Conditions	Day 0	Day 3	1 week	2 weeks	1 month	2 months	3 months
25°C/60% RH (closed container)	97.5	97.5	97.4	97.3	97.4	97.4	97.4
40°C/75% RH (open container)	97.5	97.5	97.4	97.4	97.4	97.4	97.4
80°C (closed container)	97.5	97.4	97.2	96.9	96.6	94.6	93.4

Listed as % remaining in LC purity. Note that closed container means that the substance was not exposed to RH, even if the vial was placed in that climate.

Table 7 . Solubility and stability in solution of AZD2738 chloride at room temperature.

Conditions	pH 1	pH 5	pH 7.4	Water
Concentration (mM)	>50	>50	>50	>50
Purity, 1 day, listed as % remaining in LC purity	97.0	97.0	97.0	97.1
Purity, 1 week, listed as % remaining in LC purity	96.6	96.8	96.6	96.8
pH of buffer before the substance was added	1.08	5.01	7.40	6.0
pH of solution when the substance was added	1.06	4.38	3.66	2.41

Listed as % remaining in LC purity. Four different solutions, 0.1 M HCl with pH 1, 0.1 M acetate buffer with pH 5, 0.1 M phosphate buffer with pH 7.4 and pure water, were used. Note that pH decreased due to the negative counter-ion.

Table 8 . Solubility and stability in solution of AZD2738 maleate at room temperature.

Conditions	pH 1	pH 5	pH 7.4	Water
Concentration (mM)	>50	35.0	44.5	25.7
Purity, 1 day, listed as % remaining in LC purity	97.0	96.3	97.1	97.2
Purity, 1 week, listed as % remaining in LC purity	96.6	96.8	96.9	97.0
pH of buffer before the substance was added	1.08	5.01	7.40	6.0
pH of solution when the substance was added	1.41	4.40	3.68	2.79

Listed as % remaining in LC purity. Four different solutions, 0.1 M HCl with pH 1, 0.1 M acetate buffer with pH 5, 0.1 M phosphate buffer with pH 7.4 and pure water, were used. Note that pH decreased due to the negative counter-ion.

Table 9 . Solubility and stability in solution of AZD2738 fumarate at room temperature.

Conditions	pH 1	pH 5	pH 7.4	Water[a]
Concentration (mM)	37.6	18.7	10.3	2.9
Purity, 1 day, listed as % remaining in LC purity	95.7	92.6	92.2	85.8
Purity, 1 week, listed as % remaining in LC purity	93.1	93.6	91.8	84.0
pH of buffer before the substance was added	1.08	5.01	7.40	6.0
pH of solution when the substance was added	1.92	4.30	4.15	3.48

Listed as % remaining in LC purity. Four different solutions, 0.1 M HCl with pH 1, 0. 1 M acetate buffer with pH 5, 0.1 M phosphate buffer with pH 7.4 and pure water, were used. Note that pH decreased due to the negative counter-ion.
[a]The crystal form of the substance had changed according to X-ray analysis.

solutions of the neutral form (if the amorphous substance is used, the higher degree of impurities may be an issue) or a solution of a crystalline salt (see below). Both saline and mannitol could be used as tonicity modifiers. The formulations should be preferably stored frozen at pH >3 and used within 1 month.

Salt screen

A requirement for the development of an oral solid dosage form is that the compound is possible to handle as bulk and that the solid-state stability (both chemical and physical) is acceptable. Additionally, it must be possible to manufacture and store a dosage form containing the compound. This means that the solid form of AZD2738 has to be improved. In order to find a crystalline form of AZD2738, salts were produced in a salt screen. In this screen, salts of maleic acid, fumaric acid and HCl were found. These salts were scaled up (1–2 g) and obtained as crystalline materials. Characterized physical properties of these three salts are summarized in Table 3.

AZD2738 fumarate

The fumarate salt was produced mostly as a crystalline white powder. Two different polymorphs had been identified (Figure 2, Table 3). Conversion from the metastable form to the more stable form occurred during solubility tests in water at room temperature (see below and Table 9). The melting points of the two forms are 191°C for the metastable form and 195°C for the more stable form. This indicates that the two forms are monotropic between room temperature and the melting point. The more stable polymorph is an anhydrate with a very slight weight loss (~0.2%) during heating to below the melting point. Above the melting point, the material decomposes. The material is slightly hygroscopic with a water uptake of 0.9% from 0% RH to 80% RH.

AZD2738 maleate

The maleate salt of AZD2738 was obtained as a crystalline white powder. The salt has a melting point onset of 145°C (Table 3). It is an anhydrate with a weight loss of ~0.1% during heating to below the melting point. The material is slightly hygroscopic with a water uptake of 0.7% from 0% RH to 80% RH.

AZD2738 chloride

The chloride salt was produced as a crystalline white powder (Figure 3). The material has a melting point onset of 196°C (Table 3). It is likely to be an anhydrate with a weight loss of ~0.1% upon heating to 110°C. Above 110°C, a continuous weight loss indicate that decomposition may start below the melting point. The material is slightly hygroscopic with a water uptake of 0.9% from 0% RH to 80% RH.

Solid-state stability

AZD2738 as fumarate and chloride salts are chemically stable in 25°C/60% RH, in 40°C/75% RH and at 80°C for 3 months (Tables 4 and 5). Also the maleate salt of AZD2738 is stable in 25°C/60% RH and in 40°C/75% RH for 3 months. However, at 80°C, about 4% of the tested sample had degraded after 3 months (Table 6). A degradation product was formed and eluated after 19.7 min (2%). Five more peaks increased, but were still ≤1% (>20 min). There is no correlation between the degradation patterns

formed after solid-state and solution stability (see above and below).

XRPD experiments were performed on the fumarate salt samples after 3 months (in 40°C/75% RH and at 80°C). They appeared to consist of a mix of the two earlier observed forms (see above). XRPD investigations were performed also on the maleate salt and the chloride salt (after the same conditions as above). No changes in solid state were observed for the maleate salt and the chloride salt.

Solubility and stability of the three salt forms of AZD2738

The three different salts were tested for solubility in four different solutions, 0.1 M HCl with pH 1, 0.1 M acetate buffer with pH 5, 0.1 M phosphate buffer with pH 7.4

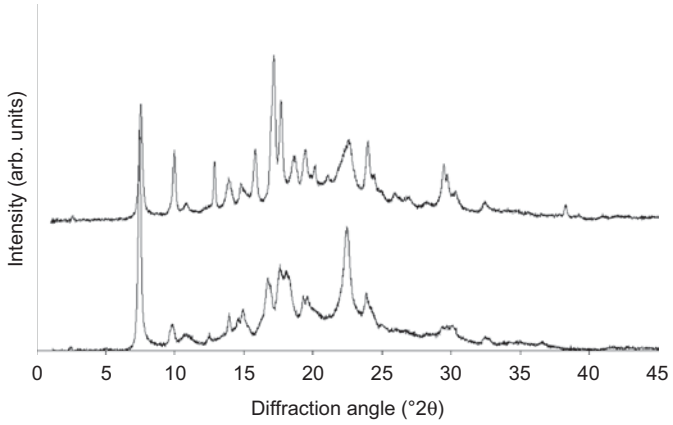

Figure 2 . X-ray powder diffractogram of AZD2738 fumarate, the most stable polymorph (bottom) and the metastable form (top).

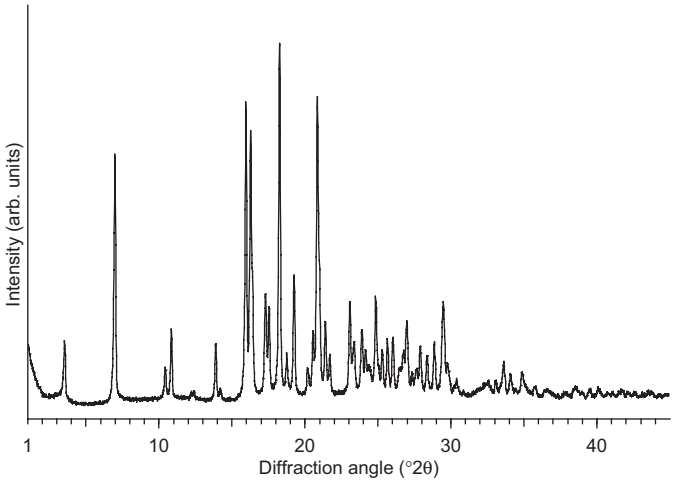

Figure 3. X-ray powder diffractogram of AZD2738 chloride.

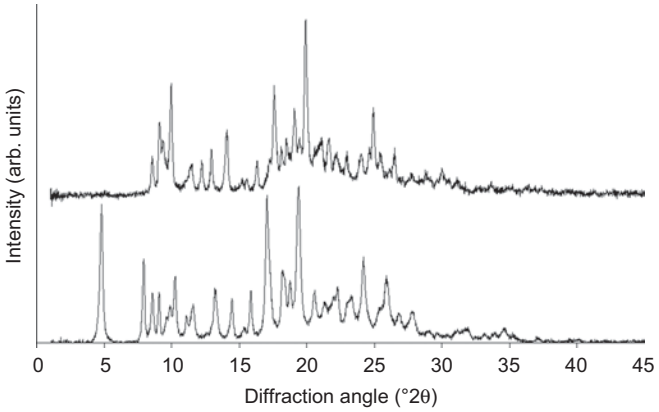

Figure 4. X-ray powder diffractograms of the two forms of AZD2738 maleate, the original form (bottom) and the form obtained in certain slurry experiments, see text (top).

and pure water. The maximum concentration of the solutions was 50 mM. If all added substance was dissolved, the solubility was set to >50 mM. The solubility is high for all salts with the exception of the fumarate salt of the substance (Tables 7–9). Both the maleate and chloride salts of AZD2738 are stable for at least 1 week at all conditions. However, analyses of the fumarate salt indicated an obvious degradation at pH 1 and in water. At both conditions, the peaks at 17.2 and 17.4 increased (see above) as well as a peak at 15.6 min (just in water).

The remaining solid material from the solubility experiments in water was analyzed with XRPD. No change in solid form was observed for the maleate salt. However, the fumarate salt was changed in a similar way as described above.

Slurries

In order to get information regarding whether other crystal forms of the three salts exist, some initial slurry experiments were performed. Suspension crystallization was carried out at room temperature in water, ethanol, methanol, 2-propanol, isooctane, n-heptane, ethylacetate, acetone, acetonitrile, chloroform, THF, EMK and MIBK. In the case of the fumarate salt, for which two polymorphs already were known (see above), the most stable form was used as starting material. The products were analyzed with XRPD after 2 weeks.

In the case of the fumarate and chloride salts, no phase transformation was observed for any of the samples.

In the case of the slurries of the maleate salt, a second crystal form was obtained in methanol, ethanol, *i*-propanol, acetone, acetonitrile, EMK, THF and chloroform. From DSC analysis, the melting point onset for this form is determined to 135°C. This indicates that the two forms are enantiotropically related between room temperature and melting point. X-ray powder diffractograms for both polymorphs of AZD2738 maleate are displayed in Figure 4.

Conclusion

This work demonstrates that compounds like AZD2738 and its degradation products can be successfully analyzed by the present LC methods. The methods have proven to be well suited for routine applications as well as required stability studies during early development. The stability of AZD2738 in liquid formulations is good (especially at pH >3), but the formulations should be stored frozen, mainly to reduce the risk of microbiological growth. The initial amorphous substance was not possible to use for further development. However, by using a salt screen approach, some crystalline salts were obtained. The solid-state stability of the investigated salts (fumarate, maleate and chloride) of AZD2738 is promising for further product development, with the chloride as the preferred counter-ion.

The stability results and the physicochemical properties of the salts of AZD2738, indicate that the substance fulfills basic requirements for further development of an IR dosage form.

The substance is highly soluble and permeable (data not shown), which gives AZD2738 the potential for classifying the drug as a class I compound according to Biopharmaceutics Classification System. Then AZD2738 may be a biowaiver, i.e. permission from the regulatory authority to use *in vitro* dissolution tests as a surrogate for *in vivo* pharmacokinetic data when assessing bioequivalence[29–31]. This can reduce risk and simplify documentation between different clinical trial formulations and/or future marketed product.

Declaration of interest

The authors report no conflicts of interest.

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