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The single crystals of eletriptan hydrobromide for two polymorphs α and β were developed to study their structural properties. The forms crystallized in monoclinic system with noncentrosymmetric space group. The molecular structure confirms eletriptan to exist as a hydrobromide salt in 1:1 ratio. In α-form, the indole nitrogen participates in intermolecular hydrogen bonding with O=S=O, the bromine anion forms a bond only with nitrogen of pyrrolidine moiety. Whereas in β-form, the bromine anion forms a bond with the nitrogen of pyrrolidine and also to indole nitrogen (N_2–H–Br . . . N_1–H). The two α and β polymorphs exhibit conformational polymorphism. The polymorphs of eletriptan hydrobromide also showed different solid state characteristic properties confirmed by using different solid state techniques such as the powder X-ray diffraction, Single crystal analysis, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), FTIR, and microscopy as well as variable humidity and temperature powder X-ray diffraction (VTPXRD).

Keywords Eletriptan hydrobromide; Conformational polymorphs; crystal structures; physico-chemical characterization

Introduction

The phenomenon of polymorphism has been recognized as an important and relevant topic in drug development, and the identification and characterization of the "desired polymorph" are regarded as critical to ensure a reliable and robust manufacturing process of an active pharmaceutical ingredient (API) [1]. This requirement emerges from the fact that different polymorphs exhibit more or less distinct material properties which may become noticeable

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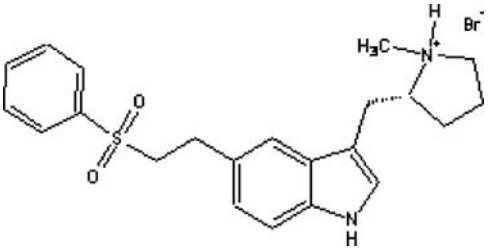

Scheme 1. Structure of Eletriptan hydrobromide.

during processing, formulation and stability testing and particularly in the case of less water soluble compounds in dissolution and bioavailability problems of the drug product [2]. One such drug substance is eletriptan hydrobromide.

Eletriptan, {3-([1-methylpyrrolidine-2®yl]methyl)-5-(2-phenyl sulphonylethyl)-1H-indole,} (see Scheme I) is classified as a 5-$HT_{1B/1D}$ receptor agonist and is particularly useful for the treatment of migraine and for the prevention of migraine recurrence. The compound has been marketed under the tradename RELPAX (Pfizer, USA). The synthesis of eletriptan hydrobromide α and β forms is discussed in the literature in which the final solvent used for crystallisation is acetone or ether solvent and aqueous acetone for β and α forms respectively. The powder X-ray diffraction pattern for α and β forms are also reported [3]. The eletriptan hydrobromide monohydrate polymorph preparation is discussed in the literature where eletriptan is treated with water, or in a suitable organic solvent containing a sufficient amount of water to facilitate formation of monohydrate [4]. Characterization of polymorphs in pharmaceuticals is a very important aspect of drug development and manufacturing [5–8]. According to ICH guidelines, active pharmaceutical ingredients (APIs) must be screened for polymorphism [9].

Our extensive literature search provided no reports on the crystal structures of α and β forms. Moreover, our literary review revealed the lack of clarity in the disclosed powder X-ray diffraction data. Hence, our investigations lead to the development of their crystals along with the structural features. The present study also relates to the novel crystallization processes for the preparation of the α and β forms and the solid state characterization of the polymorphs of eletriptan hydrobromide α and β using different analytical techniques such as the powder X-ray diffraction, Single crystal X-ray diffraction, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), FTIR, Dynamic Vapour Sorption analysis (DVS), and microscopy as well as variable humidity and temperature powder X-ray diffraction (VT-PXRD). Our study is also extended to the stress stabilities of the polymorphs of eletriptan hydrobromide, and to the molecular structure of α and β forms, including the comparative study of the two polymorphs α and β with the monohydrate.

Experimental

Materials

The polymorphic forms of eletriptan hydrobromide, viz. α, β, and monohydrate were obtained from the Chemical Research Division of Mylan Laboratories Limited. The monohydrate polymorph was analysed as such.

Crystallisation of Eletriptan Hydrobromide α-Form and β-Form. The single crystals for eletriptan hydrobromide were attempted using various solvents including methanol and

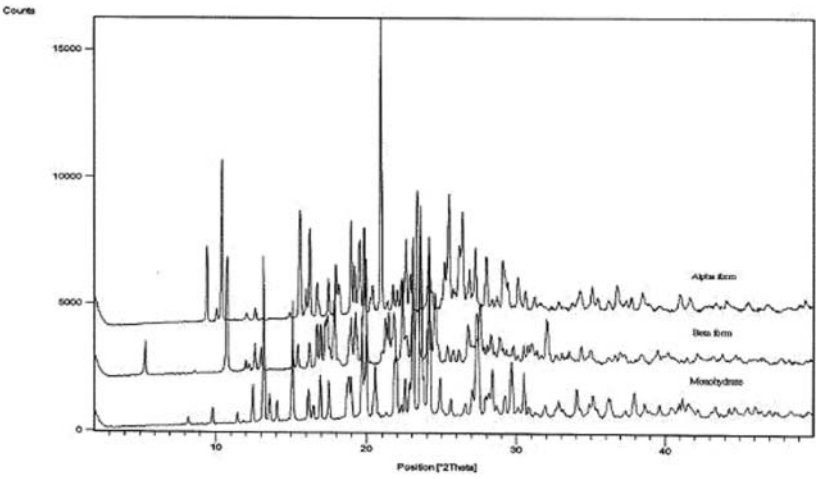

Figure 1. PXRD overlay of Eletriptan hydrobromide α-form, β-form and monohydrate.

methyl tertiary butyl ether (MTBE). However, suitable crystals could not be obtained. Suitable single crystals were obtained by using anhydrous solvents which were dried using molecular sieves and in inert atmosphere by using nitrogen atmosphere. Thusm single crystals were developed for the α form using anhydrous methanol and MTBE by slow evaporation under nitrogen atmosphere at ambient conditions. The single crystals were also developed for β form from anhydrous methanol and MTBE by slow evaporation under nitrogen atmosphere and at refrigerated conditions.

Methodology/Instruments

Powder X-Ray Diffractometry. The X-ray powder diffraction (PXRD) patterns were obtained with a PANalytical X'Pert PRO diffractometer equipped with a θ/θ goniometer using Cu-anode, automatic divergence slit and X'celerator detector. Data was collected at a tube voltage of 40 kV and a tube current of 30 mA, at a scan step of 0.03° in the angular range of 2θ of 2°–50°. The instrument was calibrated by using Corundum (NIST standard SRM 1976) for checking the angular position.

Variable Temperature X-Ray Powder Diffractometry. Samples were measured using a variable temperature PXRD, Bruker axs D8, Discover. The VT-PXRD experiments were performed with Cu Kα1 radiation using Varioα1 monochromator and Lynx Eye detector. The angular range was 2°–50° with a step size of 0.03°. The humidity and temperature was controlled by *ANSYCO Sycos H-Hot*. The samples were measured at different temperatures up to 170°C with a heating rate of 0.2°C/s. The sample holder was placed in an air-tight, thermally insulated chamber provided with an inlet and outlet for nitrogen purge gas at a controlled humidity.

Single Crystal Diffractometry. Single crystal X-ray diffraction measurements for α form were made using Bruker SMART CCD diffractometer equipped with Molybdenum-anode. X-ray tube was operated at 50 kV and 30 mA. The stereochemistry of the molecule was observed by using PLATON [10].

Table 1. List of 2θ values of the three polymorphs of Eletriptan hydrobromide

Eletriptan hydrobromide α-form			Eletriptan hydrobromide β-form			Eletriptan hydrobromide Monohydrate		
Literature 2θ values	Experimental 2θ values	Relative Intensity I/Io	Literature 2θ values	Experimental 2θ values	Relative Intensity I/Io	Literature 2θ values	Experimental 2θ values	Relative Intensity I/Io
9.7	9.5	26.11	11.0	10.8	71.04	13.2	13.2	80.49
10.7	10.4	53.5	17.2	17.3	31.14	15.1	15.1	55.02
15.9	15.6	35.32	19.2	19.3	33.16	17.0	17.0	23.75
16.5	16.3	30.4	20.1	19.9	62.19	19.7	19.7	49.56
17.8	18.0	18.45	21.6	21.9*	29.82	20.0	20.0	40.49
18.3	18.1	11.97	22.6	22.7	16.74	20.6	20.6	27.12
19.3	19.2	17.95	23.6	23.4	100	21.9	21.9	29.66
19.8	19.8	31.07	24.8	24.6	38.1	22.0	22.0	30.74
20.1	20.2	7.27				23.1	23.1	83.21
21.2	20.9	100				23.6	23.6	100
24.4	24.3	9.35				24.1	24.1	91.8
25.5	25.4	42.38				27.3	27.3	48.48
25.8	25.8	10.33				29.7	29.7	29.01
26.7	26.4	36.15						
27.6	27.3	24.18						
29.4	29.4	12.65						

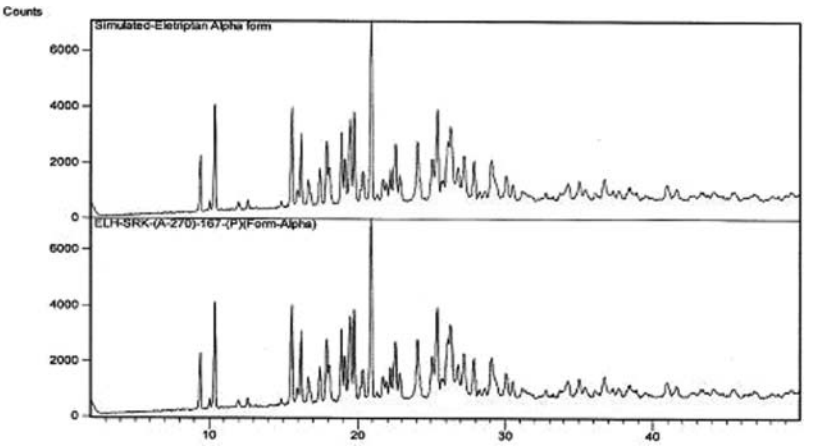

Figure 2. PXRD overlay of Eletriptan hydrobromide α-form overlaid with the simulated powder pattern.

Single Crystal Diffractometry. Single crystal X-ray diffraction measurements for β form were made using Rigaku Mercury 375R CCD diffractometer equipped with Molybdenum-anode. X-ray tube was operated at 50 kV and 12 mA. The stereochemistry of the molecule was observed by using PLATON [10].

Fourier Transform Infrared (FTIR) Spectroscopy. FTIR spectra were obtained with Perkin–Elmer Spectrum One spectrometer. The samples were prepared on KBr disks and the spectra were collected over a spectral range of 4000 to 500 per cm, resolution of 4 per cm and 16 number of scans. The instrument is calibrated by using NIST standard 1921 polystyrene.

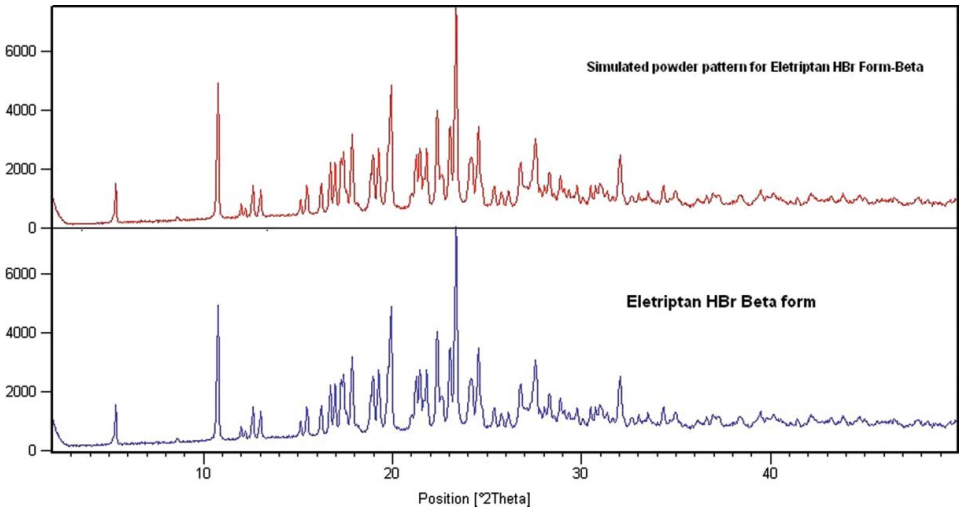

Figure 3. PXRD overlay of Eletriptan hydrobromide β-form overlaid with the simulated powder pattern.

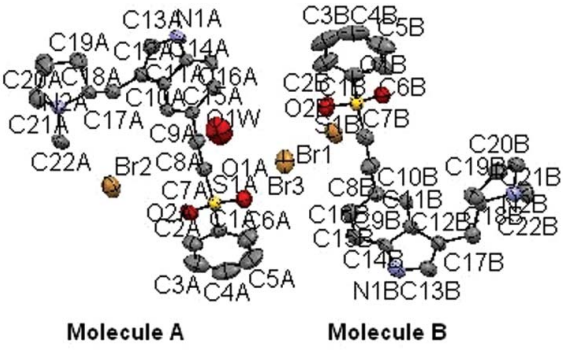

Figure 4. ORTEP diagram of Eletriptan HBr Form-α.

Differential Scanning Calorimetry. DSC thermograms were recorded with Q1000, TA Instruments. Approximately 1–3 mg of the sample was weighed into standard aluminum pans and crimped with a lid. Dry nitrogen was used as purge gas at a flow rate of 50 ml/min. Data was collected at a heating rate of 10°C/minute over a temperature range of 30°C to 300°C. The temperature and enthalpy calibration for the instrument was performed with pure indium (mp 156.6°C, heat of fusion 28.45 J/g).

Thermogravimetric Analysis. TGA was performed with Q5000IR, TA Instruments. Samples of approximately 3–5 mg were placed on a pre-weighed aluminum pan. Temperature calibration of the instrument was performed using a ferromagnetic material such as nickel. The Curie-point temperature was measured and the instrument calibrated. Dry nitrogen was used as purge gas at a flow rate of 25 mL/min. Data was collected at a heating rate of 10°C/min over a temperature range of 30°C to 300°C.

Dynamic Vapour Sorption Analysis. DVS analysis were performed on Intelligent Gravimetric Sorption Analyser (IGAsorp), Hidem Isochema Instruments. Samples were collected by exposing to humidities in the range of 0%–90% RH and 90%–0% at 35°C for Monohydrate sample, and for α form, it was collected from 10% to 75% RH at 35°C.

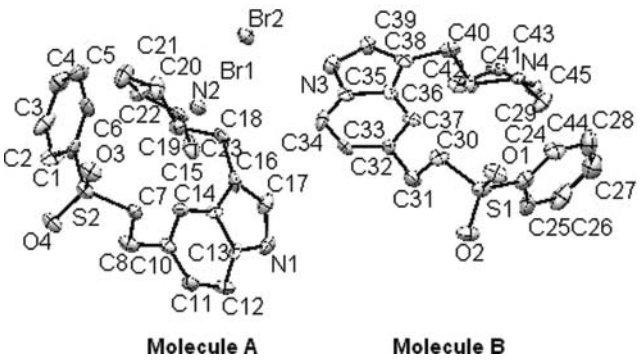

Figure 5. ORTEP diagram of Eletriptan HBr Form-β.

Table 2. Crystallographic information of the Eletriptan hydrobromide α- and β- Forms

Crystallographic Parameters	Details	
Name of the molecule	Eletriptan HBr (α-form)	Eletriptan HBr (β-form)
Empirical Formula	$C_{22}H_{27}N_2O_2S.Br$	$C_{22}H_{27}N_2O_2S.Br$
Molecular Weight	463.43	463.43
Crystal System	Monoclinic	Monoclinic
Space Group	C2	$P2_1$
Lattice Type	—	—
Cell Parameters		
a (Å)	18.224(2)	12.523(3)
b (Å)	10.8981(14)	10.594(2)
c (Å)	22.204(3)	16.223(3)
$\alpha = \gamma$ (°)	90°	90°
β (°)	95.352(2)	92.31(3)
Volume ($Å^3$)	4390.7 (10)	2150.5(8)
Z value	8	4

Cif files for both the forms is submitted in the supplementary information. CCDC-806053 (β-Form), CCDC-806079 (α-Form), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and Discussion

Powder X-Ray Diffractometry

The experimental powder pattern for the three polymorphs of eletriptan hydrobromide is shown in Fig. 1. The eletriptan hydrobromide polymorphs exhibited characteristic patterns with prominent peaks at the following angular positions as in Table 1. The simulated powder pattern for the polymorphs of eletriptan hydrobromide α-form and β-form, obtained from the crystallographic data was found to be comparable to the experimental powder pattern

Table 3. Torsion angles (°) for of α- and β-forms for two independent molecules

	Eletriptan hydrobromide α-form torsion angle(°)		Eletriptan hydrobromide β-form torsion angle(°)	
	Molecule-A	Molecule-B	Molecule-A	Molecule-B
C20−C19−C18−N2*	25.5(7)	26.2(6)	0.6(14)	−11.7(11)
C19−C18−N2−C21*	−41.2(6)	−43.4(6)	26.1(12)	−15.9(11)
C18−N2−C21−C20*	41.3(7)	43.0(6)	−41.8(11)	36.2(11)
N2−C21−C20−C19*	−24.2(8)	−25.1(7)	41.2(12)	−42.9(11)
C21−C20−C19−18*	−1.3(9)	−1.4(7)	−26.5(14)	34.7(12)
C1−S1−C7−C8	177.3(4)	−177.4(5)	−82.5(8)	85.0(9)

*Torsion angles of the pyrrolidine ring.

Table 4. Hydrogen-bond geometry (Å,°) of α-form

D—H . . . *A*	D—H	H . . . *A*	D . . . *A*	D—H . . . *A*
N1A H1A O2A[i]	0.86	2.13	2.933(6)	154.2
N1B H1B O1B[ii]	0.86	2.30	3.049(6)	145.3
N2B H2B1 Br3[iii]	0.91	2.45	3.287(5)	153.1
N2A H2A1 Br3	0.91	2.35	3.201(5)	155.8

Symmetry codes: i) 'x+1/2, y+1/2, z'+1, ii) 'x+1/2, y+1/2, z', iii) 'x, y+1, z'+1.

thereby confirming the powder X-ray diffraction data of eletriptan hydrobromide α-form and β-form (Figs. 2 and 3). The simulated powder pattern was found to be comparable to that reported previously [3]. However, the ambiguity in the characteristic peaks disclosed in the same literature was clarified based on the crystallographic data obtained.

Structural Features of the Polymorphs

The eletriptan hydrobromide α-form, crystallizes in the monoclinic crystal system with asymmetric space group C_2, whereas the β form crystallizes also in the monoclinic crystal system but with asymmetric space group $P2_1$. The crystal structure of eletriptan hydrobromide monohydrate is reported in literature [4, 11]. The molecular structure for α and βforms consists of eletriptan base cation and bromide anion existing as hydrobromide salt in 1:1 ratio. The unit cell is asymmetric comprising of two independent molecules, Molecule A and Molecule B as in Figs. 4 and 5 for α and β polymorphs. The two polymorphs were differentiated by the orientation of bromine atom with base. The crystallographic parameters for the two polymorphs were listed in Table 2.

Conformational Polymorphism in α and β Forms

According to the author Corradini [12] conformational polymorphism is the existence of different conformers of a molecule in the same molecule in different polymorphic modifications, a situation which can arise when there is more than one molecule in the asymmetric unit cell. Similar type of polymorphism is seen in both α and β forms. The important torsion angles for eletriptan hydrobromide polymorphs α and β are listed in Table 3. The Pyrrolidine ring is in envelope conformation in polymorph α for Molecules A and B which is also seen in monohydrate polymorph [11], whereas in Molecule B of β –form, the pyrrolidine ring assumes half chair conformation.

Table 4a. Hydrogen-bond geometry (Å,°) of β-form

D—H . . . *A*	D—H	H . . . *A*	D . . . *A*	D—H . . . *A*
N1 H1 Br1[i]	0.8800	2.4900	3.372(10)	176.00
N2 H2N Br2	0.61(9)	2.64(9)	3.234(10)	167(12)
N3 H3A Br2	0.8800	2.6700	3.462(10)	151.00
N4 H4N Br1[ii]	0.77(9)	2.43(9)	3.194(9)	173(13)

Symmetry codes: i) –x+1, 1/2+y, −z+1, ii) −x, 1/2+y, −z+1.

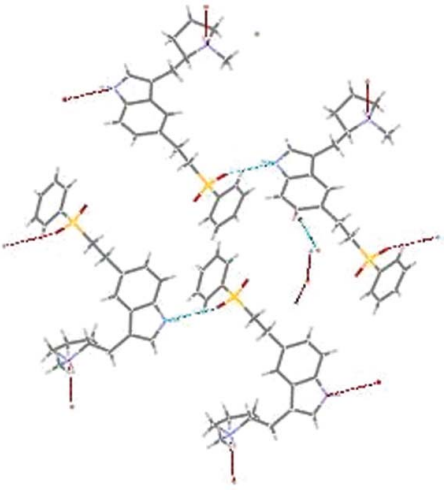

Figure 6. Hydrogen bonded chain along the c-axis for α-Form.

Indole moiety conformation in both the molecules, the methyl group on pyrrolidine ring is in *cis* conformation, that is, (C22A-N2A-C18A-C17A) ~66.83° and (C22B-N2B-C18B-C17B) ~64.31°. In β-form, the methyl group on the pyrrolidine ring is in *cis* conformation with slight differences in the torsion angle (C23-N2-C19-C18) ~70.72° and (C45-N4-C41-C40) ~93.57° which can be attributed to the ***synclinal*** stereochemical arrangement [13].

The α and β forms also differ from each other by the orientation of groups in crystal structure, that is, the connecting chain of the phenyl and sulphoxide group with the indole moiety is showing *trans* conformation in α-form of both the Molecules A and B with torsion angles (C1A-S1A-C7A-C8A) ~177.28° and (C1B-S1B-C7B-C8B) ~177.50° respectively. However, in β-form for both the molecules A and B, the phenyl and sulphoxide group is oriented with indole moiety in *cis* conformation having a torsion angle (C1-S2-C7-C8)

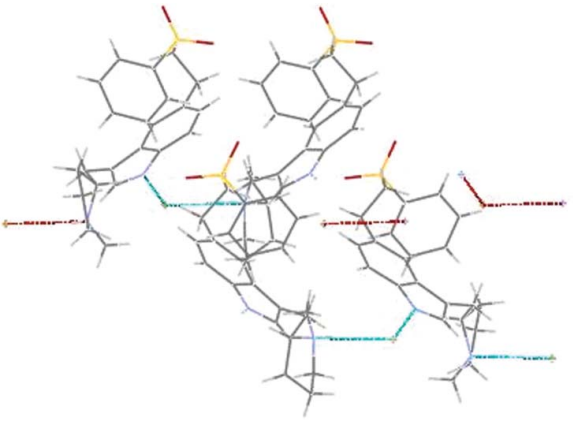

Figure 7. Hydrogen bonded chain along the c-axis for β-Form.

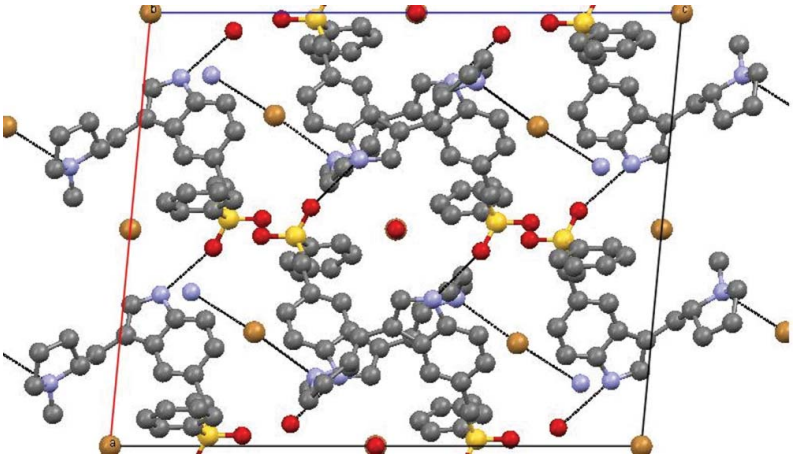

Figure 8. The Packing Diagram of Eletriptan hydrobromide Form-α illustrates the head to tail hydrogen bonding.

$\sim$82.52° and (C24-S1-C30-C31) $\sim$84.97° respectively. Due to this conformational difference the Molecules A and B in β-form are semicircular, whereas in α-form, the Molecules A and B are arranged in head to tail manner. Based on the conformational difference between α and β forms conclude that the two polymorphs are related to conformational polymorphism.

Inter-Molecular Hydrogen Bonding

Intermolecular hydrogen bonding observed in both the forms as shown in Tables 4 and 4a. Two symmetry independent molecules for both the forms are connected via strong hydrogen bonds to form ribbons along the c-axis of the unit cell as in Figs. 6 and 7.

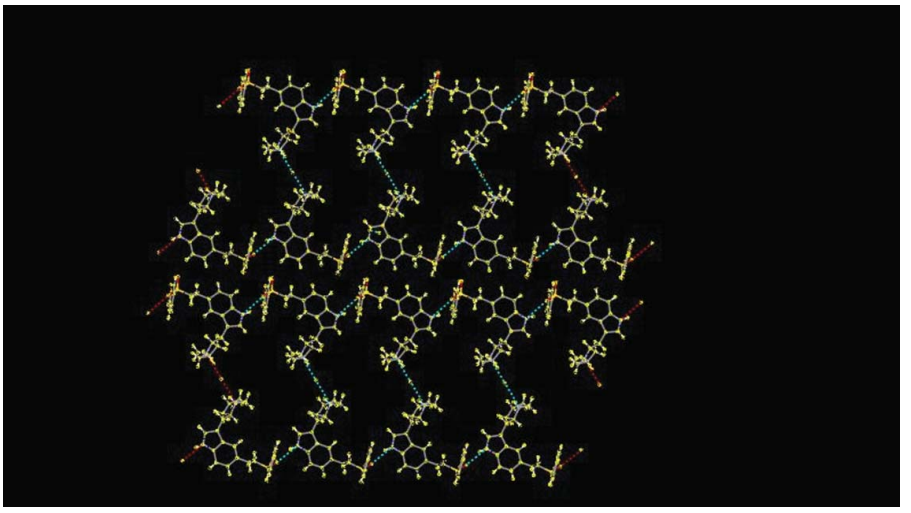

Figure 8a. Illustrates the packing mode of Eletriptan hydrobromide α-form.

Table 5. IR absoption bands of the three polymorphs of eletriptan hydrobromide

Mode of vibration	Wave number (cm^{-1}) for α-form	Wave number (cm^{-1}) for β-form	Wave number (cm^{-1}) for monohydrate
N—H Stretching	3372	3476, 3248	3472, 3248
Aromatic C—H Stretching	—	3016, 2994	—
Aliphatic C—H Stretching	2951, 2902, 2844	2923, 2853	2954, 2922
N^+H Stretching	2712, 2524	2638, 2542	261, 2542
C=C Stretching	1619, 1584	1647	1647
Aliphatic C—H Bending	1477, 1446, 1386	1484, 1445	1483, 1445
O=S=O Asymmetric Stretching	1343, 1307	1347, 1305	1347, 1329, 1305
C—N Stretching	1264	1288, 1267	1288, 1267
O=S=O Symmetric Stretching	1151	1152, 1141	1141
Aromatic C—H Bending	805, 740, 728	768, 748, 730	822, 807, 767, 748, 730
C—S Stretching	689, 652	689, 643	689, 643

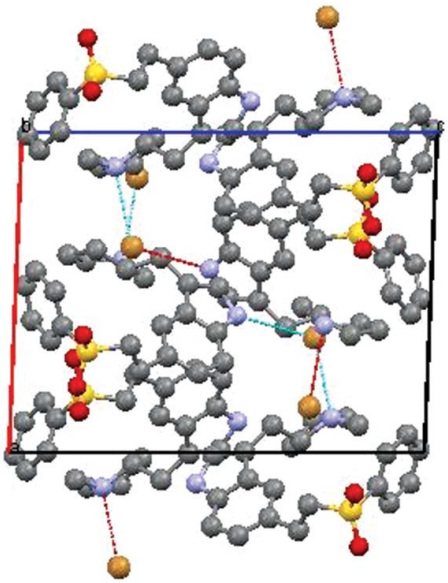

Figure 9. The Packing Diagram of Eletriptan hydrobromide Form-β illustrates the head to tail hydrogen bonding.

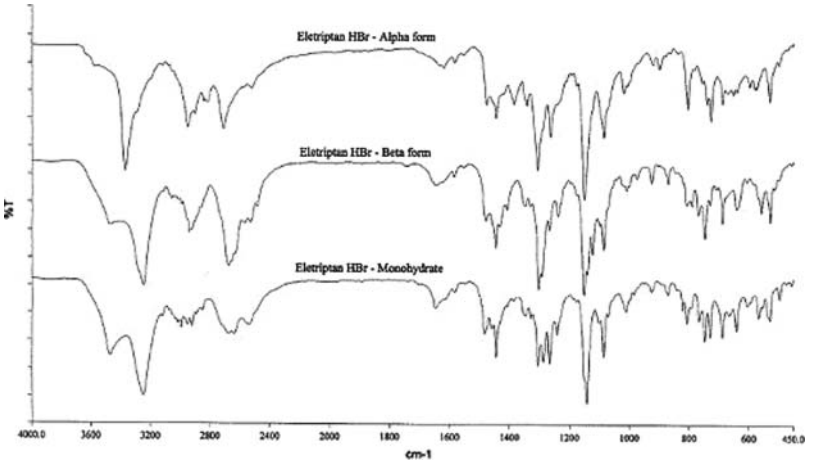

Figure 10. IR spectra of Eletriptan hydrobromide α-form, β-form and monohydrate.

In β-form, the bromine anion is linked to the nitrogen of pyrrolidine moiety and also to the indole nitrogen of the other molecule through intermolecular hydrogen bonding, In α-form, the bromine anion is linked to nitrogen of pyrrolidine moiety and to the same moiety of the other molecule. In only α-form, the water-bromine hydrogen bonding observed.

In β-form, the bonding exists between oxygen of O=S=O moiety with carbon of benzene moiety of the other molecule and carbon of pyrrolidine with oxygen of O=S=O moiety. These bonding extends along "ac" plane which sets the molecular packing intact. In α-form, there are inter molecular hydrogen bonding between oxygen of O=S=O moiety and indole nitrogen as N1A . . . . H1A . . . O2A, N1B . . . H1B . . . O1B. These bonding

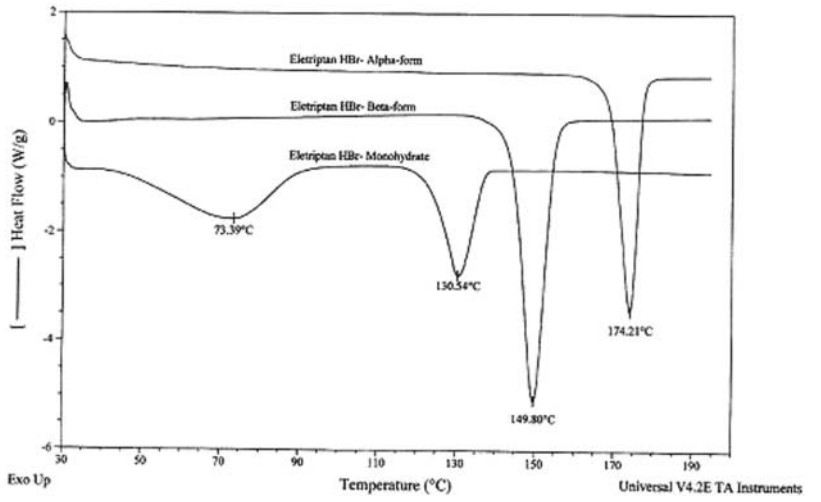

Figure 11. DSC thermograms of Eletriptan hydrobromide α-form, β-form and Monohydrate.

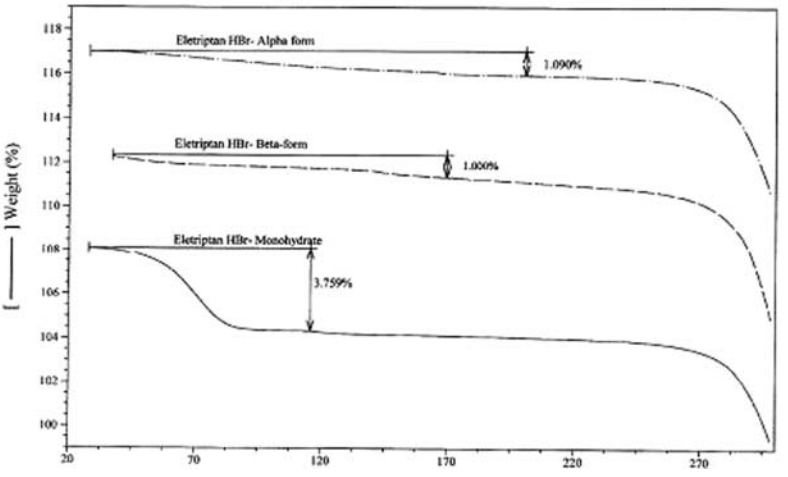

Figure 12. TGA thermograms of Eletriptan hydrobromide α form and β form and Monohydrate.

extends diagonal to the "ab" axis which sets the molecular packing intact. Pyrrolidine nitrogen has contact with bromine atom in both Molecules A and B. The packing diagrams for both polymorphs is presented as shown in Figs. 8 and 9.

In α-form, the hydrogen bonding is independently running parallel in Molecule-A and Molecule-B. Both the molecules are connected through bromine atom. The bromine is acting as a bridge atom for Molecule-A and Molecule-B which is related by translational symmetry. This bonding leads to the formation of large rings (ring graphset) or lacuna $R_6^4(37)$ as in the Fig. 8(a). But in β-form, both the molecules are connected by bromine atom through hydrogen bonding. In eletriptan hydrobromide monohydrate [11] the intermolecular hydrogen bonding extends along a-axis to form a helical chain where

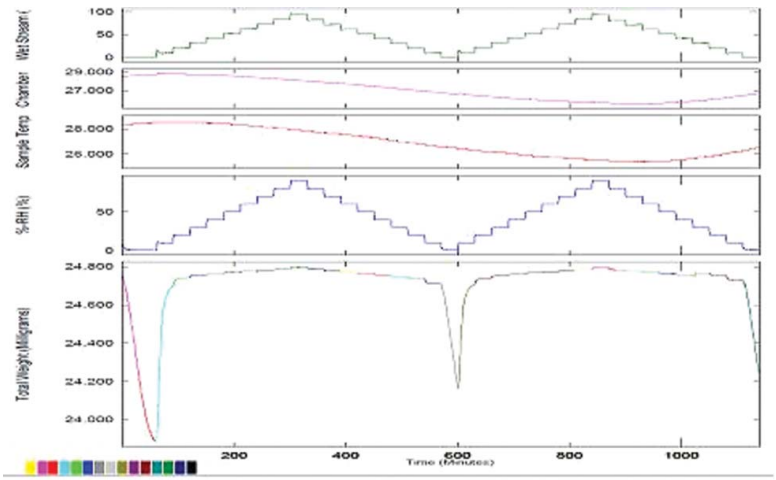

Figure 13. DVS isotherm of Eletriptan hydrobromide monohydrate.

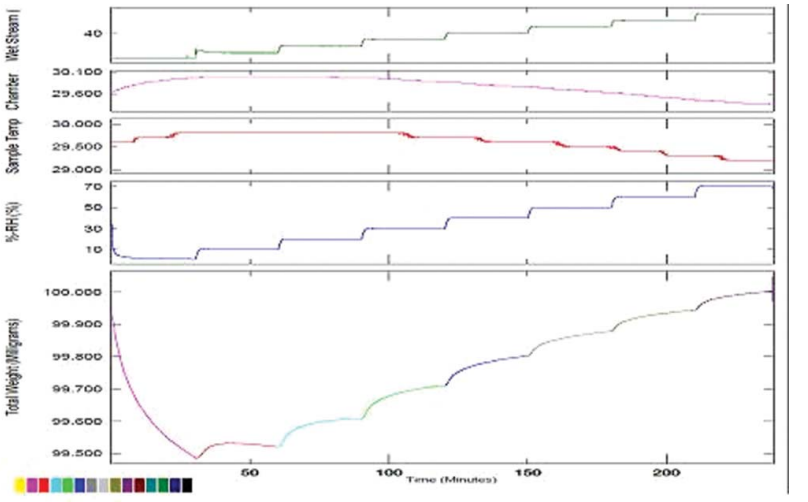

Figure 14. DVS isotherm of Eletriptan hydrobromide α-form.

water molecule forms hydrogen bonding with nitrogen of pyrrolidine group, oxygen of sulphoxide group and bromine atom.

Intra Molecular Hydrogen Bonding

It is observed only in β-form, C6 . . . H6–O3 and C29 . . . H29–O1 leading to the formation of 5-membered ring which stabilizes the molecular conformation. Intramolecular hydrogen bonding is not observed in α-form.

The stereo chemistry [14] of the molecule in both the forms is observed as "R" by using PLATON [2].

Even though the α and β forms are anhydrous, there is one water molecule observed in the crystal unit cell of α-form. Also it does not appear to participate in inter molecular hydrogen bonding. It maybe assumed that the water and the water-bromine hydrogen

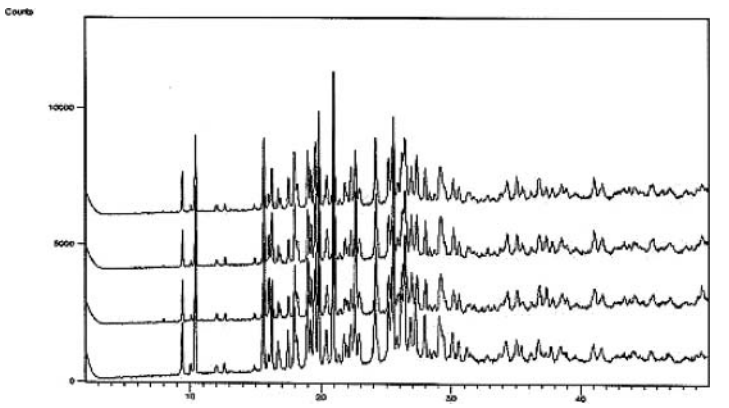

Figure 15. PXRD overlay of eletriptan hydromide α-form at 25°C for 6 M.

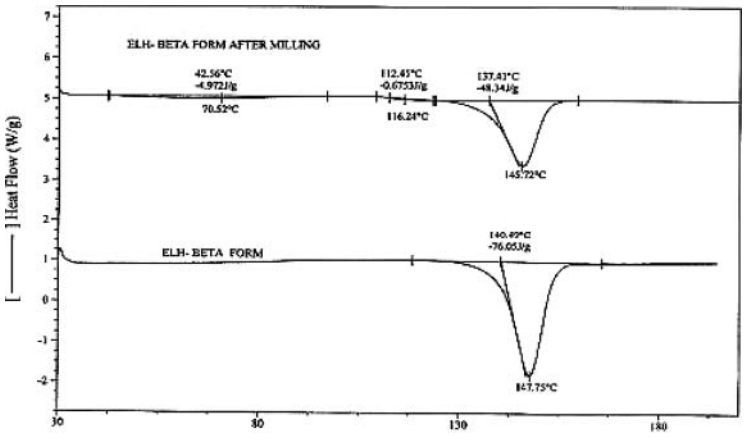

Figure 16. DSC overlay of Eletriptan hydromide β-form before and after milling.

bonding also observed, in short contact hydrogen bonding, Due to the anhydrous nature, may be the crystal might have absorbed the moisture in the crystal lattice at the time of data collection, since from the TGA, weight loss observed is only 1.3%w/w which can be attributed to moisture pickup during the data collection.

FTIR Spectroscopy

The FTIR spectra were collected for the α-form, β-form, and monohydrate polymorphs. The spectrum for each polymorph was different with characteristic absorption bands [15] as follows. The three polymorphs of eletriptan HBr salt shows the following significant absorption bands as shown in Table 5.

From the overlaid FTIR data (Table 5), the three polymorphs of eletriptan hydrobromide show characteristic difference of absorption bands in the regions of N–H and aromatic C=C stretching as shown in Fig. 10.

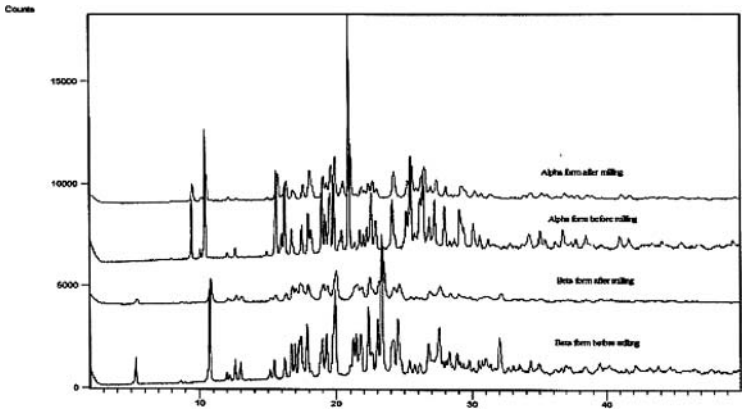

Figure 17. PXRD overlay of Eletriptan hydromide β-form and α-form before and after milling.

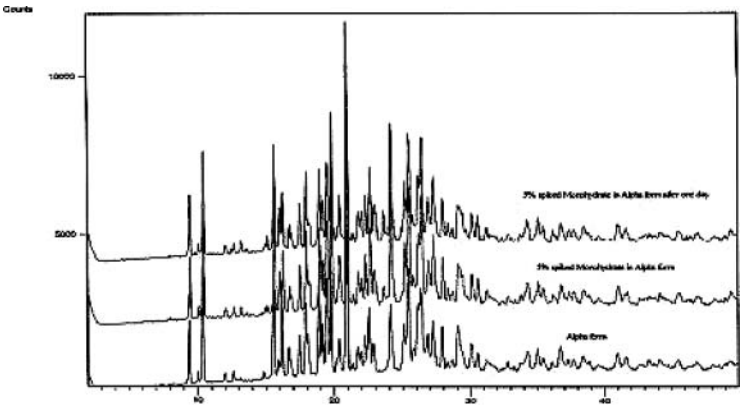

Figure 18. PXRD overlay of Eletriptan hydromide 5% spiked monohydrate in α-form.

Thermal Analysis and Dynamic Vapor Sorption Analysis

Eletriptan hydrobromide α-form, β-form, and monohydrate measured by DSC and TGA revealed the characteristic nature of each of the polymorphs. Eletriptan hydrobromide α-form, showed a single sharp endothermic peak at 172°C with no significant water loss. The β-form also showed a single sharp endothermic peak at 150°C. The DSC thermogram of eletriptan hydrobromide monohydrate shows two broad endothermic peaks at around (58°C–115°C) and at 129°C. The former peak is due to the dehydration of the monohydrate followed by the melting endotherm. The DSC overlay for the three polymorphs of eletriptan hydrobromide is presented in Fig. 11.

According to Morris and Rodriguez–Hornado [16], hydrates are crystalline materials with water incorporated into the crystal lattice. Hydrates can be of three types: channel, isolated site hydrates and ion-associated hydrates (involving a metal-ion) [16–19]. Weight loss due to dehydration below 100°C is usually associated with channel type of hydrate. Channel water exists in channels or tunnels of the crystal lattice from which solvent molecules are mobile. The water molecules come out and enter freely in to the crystal lattice. On the other hand, in lattice hydrates the lattice water is the water located inside

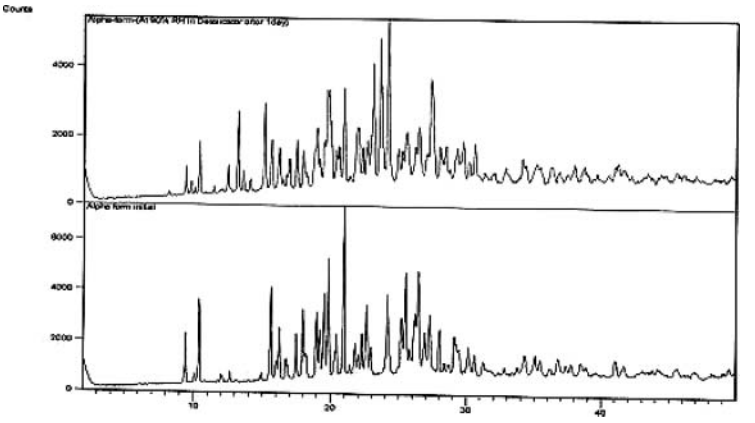

Figure 19. PXRD overlay of Eletriptan hydromide α-form exposed to 90% RH.

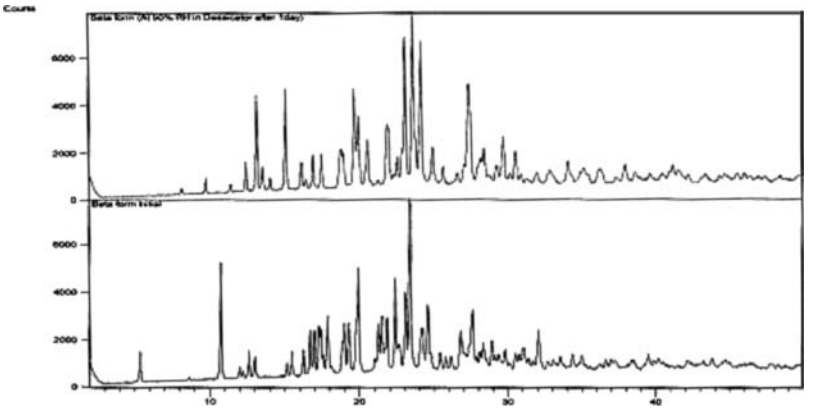

Figure 20. PXRD overlay of Eletriptan hydromide β-form exposed to 90% RH.

the crystal lattice which can be removed only by destroying the crystal lattice. In general, the water molecules in hydrates are almost always involved in the hydrogen bonding that usually contribute to the coherence of the crystal structure.

To evaluate the nature of hydration dynamic vapor sorption analysis was performed for eletriptan hydrobromide monohydrate and the data compared with the thermal analysis data. From the TGA data Fig. 12, the total water loss in eletriptan hydrobromide monohydrate is around 3.9%w/w which is comparable to monohydrate (Theoretical water content of 3.74%w/w). Figure 13 shows a consistent sorption-desorption with the stoichiometric moisture loss/uptake. The TGA data shows the dehydration of water molecule occurring rapidly in single step which is lost below 100°C, indicating eletriptan hydrobromide monohydrate to be a lattice type of hydrate [10].

Figure 14 shows the moisture sorption isotherm for eletriptan hydrobromide α-form. The sorption and desorption studies did not show any significant weight loss. The anhydrous nature for the α form of eletriptan hydrobromide is confirmed by the dynamic vapour sorption analysis. The data also proved that the water observed in the single crystal data is due to moisture pickup during data collection.

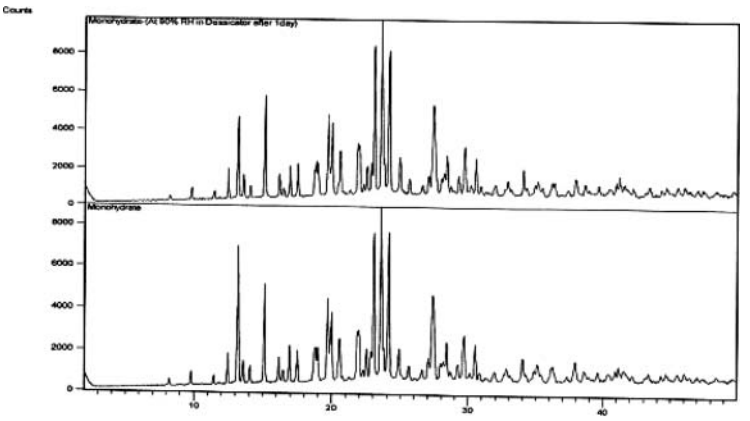

Figure 21. PXRD overlay of Eletriptan hydromide Monohydrate exposed to 90% RH.

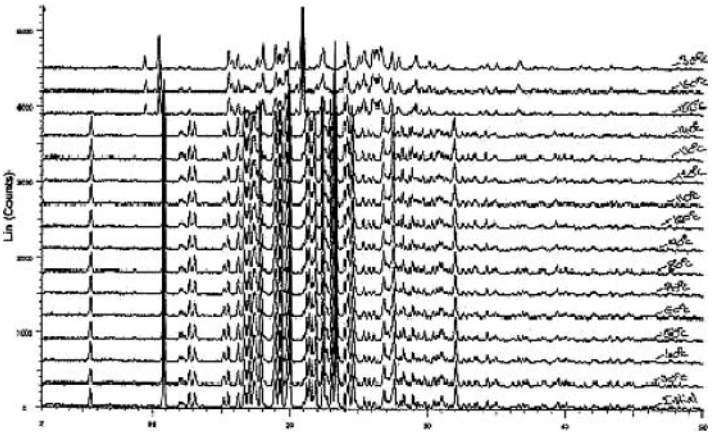

Figure 22. Variable temperature PXRD overlay of Eletriptan hydromide β-form.

Stability of Eletriptan Hydrobromide

When the polymorphs α and β of eletriptan hydrobromide stored at 25%–60% RH and 5°C ± 3°C conditions for a period of six months and were analyzed by PXRD, the polymorphs were found to be stable as in Fig. 15. From the DSC data as in Fig. 16 the β-polymorph shows slight conversion to monohydrate upon milling and reduced crystalline nature as observed from the PXRD data Fig. 17. The α-polymorph is however stable upon milling as in Fig. 17. Stability of eletriptan hydrobromide α-form spiked with 5% monohydrate was also studied under ambient conditions, but only the characteristic peaks of monohydrate are enhanced. Intensity of the full pattern is unchanged (∼6000 counts). Monohydrate content has changed by about 2%–3% as is evident from Fig. 18. Stability of the polymorphs was also studied by exposing them to 90% RH atmosphere in dessicator. The PXRD patterns of α form and monohydrate forms was unchanged whereas the β form converted to monohydrate as in Figs. 19–21—respectively.

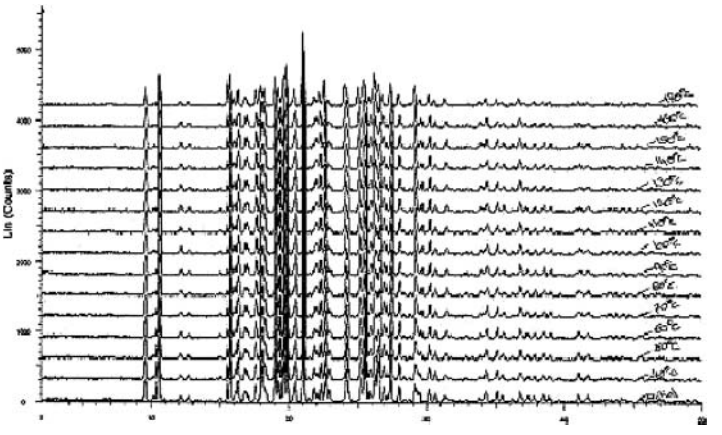

Figure 23. Variable temperature PXRD overlay of Eletriptan hydromide α-form.

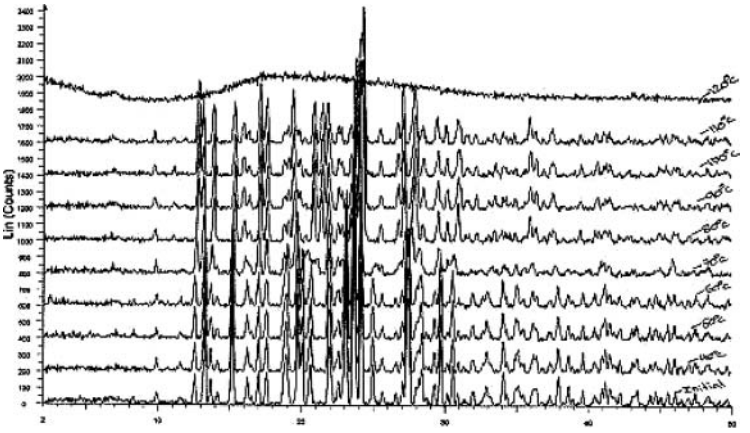

Figure 24. Variable temperature PXRD overlay of Eletriptan hydromide monohydrate.

Variable Temperature/Humidity X-Ray Powder Diffractometry

The stability of the polymorphs was also studied using the VT-PXRD and Humidity controlled PXRD. Eletriptan hydrobromide α-form, β-form, and monohydrate was subjected to temperature ranging from ambient to 170°C. An interconversion between the two polymorphs was observed between 150°C to 160°C. Eletriptan hydrobromide β-form was found to undergo conversion to α-form at a temperature of ~150°C–160°C and remained as α-Form upon cooling to 30°C as in Fig. 22. Further, the α-Form remained as such upto 170°C Fig. 23. Eletriptan hydrobromide monohydrate was found to be stable up to 110°C. It is converted to amorphous form at a temperature above 120°C Fig. 24.

Conclusions

Crystallization of eletriptan hydrobromide from methyl tertiary butyl amine and methanol resulted in the formation of stable polymorphs-two anhydrates ($\underline{\alpha}$ and β forms) respectively and the monohydrate as a lattice hydrate.

The crystal structure of eletriptan hydrobromide of both the Forms (α and β), has been determined. The packing motif indicates the importance of hydrogen bonds, even though their contribution to the total lattice energy is relatively small.

The two polymorphs were differentiated by the orientation of bromine atom with base, Pyrrolidine ring is in envelope conformation in polymorph α-Form, whereas in Molecule B of β form the pyrrolidine ring assumes half chair conformation. The α and β forms also differ from each other by the orientation of groups in crystal structure, that is, the connecting chain of the phenyl and sulphoxide group with the indole moiety is showing *trans* conformation in α-form and in β-form in *cis* conformation

The polymorphs α and β of eletriptan hydrobromide is consistent during manufacturing and stability, but milling affects the stability of the β-polymorph. The anhydrous α-form of eletriptan hydrobromide mentioned is essentially nonhygroscopic under normal conditions as is evident from the hygroscopicity studies. The anhydrous β-form of eletriptan hydrobromide is stated to be unstable and found to undergo polymorphic conversion to the monohydrate form.

The present study on the characterization of the polymorphs of eletriptan hydrobromide exemplifies the value of complementary analytical approaches to gain an understanding of the solid-state forms.

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