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Characterization of solid-state forms of mebendazole

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This study deals with the generation and characterization of various solid-state forms of mebendazole (MBZ), a benzimidazole antihelmentic. The drug was subjected to polymorphic screen using different solvents to explore the possibility of existence of different solid forms. Different reported polymorphic forms of MBZ, i.e. form A, B and C were found to be recrystallized from acetic acid : methanol mixture (1 : 1), ethyl acetate and methanol, respectively. *N*,*N*-Dimethyl acetamide (DMA) and *N*,*N*-dimethyl formamide (DMF) yielded two new solvates of MBZ. These solid-state forms were characterized by thermoanalytical (DSC, TGA, HSM), crystallographic (XRD), microscopic (optical, polarized), and spectroscopic (FTIR) techniques. Solubility studies were carried out for the solvates to identify the solubility advantage. Molecular modeling studies revealed moderately strong hydrogen bonding between the solvent molecules and MBZ.

1. Introduction

The importance of polymorphism and related solid-state phenomena is being realized in recent years, especially because of the regulatory controls which necessitate a close examination of the products under development for their solid-state behavior (Byrn et al. 1995; Threlfall 2000). Identification of all possible polymorphic forms requires thorough polymorph screening using multiple solvents and conditions (Gu et al. 2001; Mirmehrabi and Rohani 2005). Use of various solvents during purification and recrystallization of the active pharmaceutical ingredient (API), may lead to the formation of undesired solid form. Different solid forms may differ in terms of physico-chemical, mechanical and biological properties of the drug (Chawla and Bansal 2003). Hence, there is a need to identify all possible forms and control the generation of desired form. Among the various techniques of polymorphic screening like sublimation, solvent evaporation, vapor diffusion, thermal treatment, crystallization from the melt, precipitation by change of pH, growth in the presence of additives, or grinding (Guillory 1999); solvent recrystallization remains the most preferred and commonly used method.

Mebendazole (MBZ) is a popular benzimidazole antihelmintic, useful in the treatment of ascariasis, uncinariasis, trichuriasis and oxyuriasis. (Byrn et al. 1995; Tracy and Webster 2001). Three polymorphic forms of MBZ are known namely form A, B and C (Swanepoel et al. 2003). The present study involved comprehensive polymorphic screening of MBZ using different solvents. The generated solid-state forms of MBZ were characterized by thermal, crystallographic, microscopic, and spectroscopic techniques. The recrystallized products were also studied for aqueous solubility. Molecular modeling studies were carried out to understand the solute-solvent interactions within the crystal lattice of the solvated forms.

2. Investigations, results and discussion

2.1. Solubility determination of drug in solvents

Information on the solubility of a drug in various solvents is necessary for carrying out any crystallization, as the solvents showing a drug solubility of 5–200 mg/ml are considered as 'good' solvents for crystallization (Guillory 1999). Table 1 lists the solvents in which the solubility of MBZ was determined. As observed from the table, the

Table 1: Solubility values of MBZ in different solvents

Solvents	Approximate solubility values of MBZ in solvent (mg/ml)
N,*N*-Dimethyl acetamide (DMA)	20
N,*N*-Dimethyl formamide (DMF)	20
Dimethyl sulfoxide (DMSO)	25
Ethyl acetate	5
Acetic acid : methanol (1 : 1)	5
Methanol	10
Formic acid	35
Formic acid : methanol (1 : 1)	10
Water	Practically insoluble
Chloroform	<1
Carbontetrachloride	<1
Octanol	<5
Toluene	<5
Hexane	<5
Dichloromethane	<5

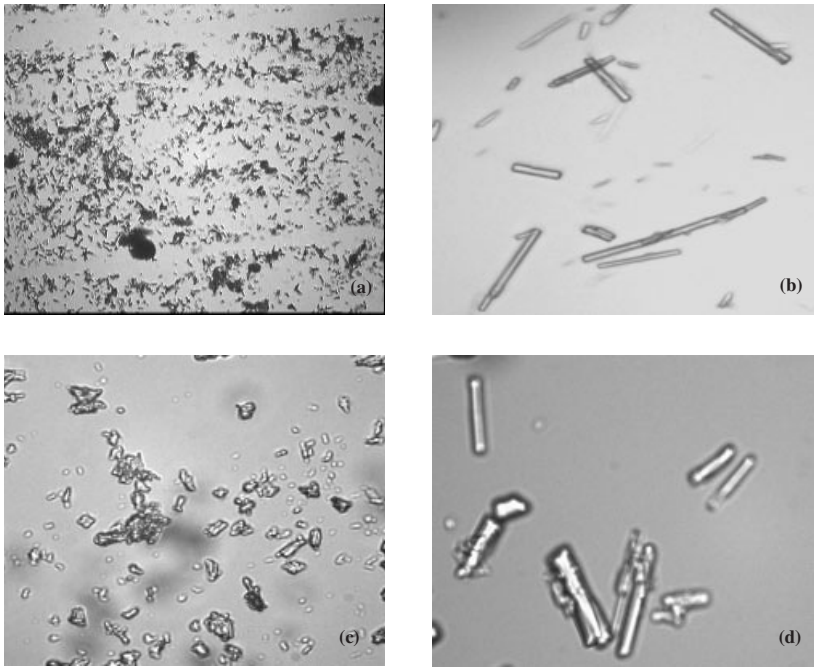

Fig. 1:
Photomicrographs (500x) of (a) pure MBZ; (b) crystals generated from acetic acid : methanol (1 : 1); (c) ethyl acetate; (d) methanol

choice of solvents for recrystallization of MBZ got limited, due to its poor solubility (less than 5 mg/ml) or degradation in certain solvents like tetrahydrofuran (THF). Recrystallization experiments were, therefore, proceeded with only those solvents in which the solubility was greater than the acceptable solubility.

2.2. Solid-state screening

The recrystallized products were characterized using a range of analytical techniques and compared to the previously reported polymorphic forms.

2.2.1. Microscopy

Crystal morphology plays a valuable role in pharmaceutical processing and product development of solid dosage forms (Chawla et al. 2003). Differences in crystal habit may strongly influence the particle orientation, flowability, packing, compaction, compressibility and dissolution characteristics of a drug powder (Tiwary 2001). The morphological features of various solid-state forms of MBZ were visually examined using optical microscopy. The stable, pharmaceutically useful MBZ occurs as fine micronized needles, while the forms recrystallized from different solvents had different habit (Fig. 1). Needles were obtained most commonly during the polymorph screening. No change in habit was seen in crystals generated using acetic acid : methanol, methanol, formic acid, dImethyl sulphoxide and formic acid : methanol mixture. Change in crystal habit was observed in ethyl acetate (irregular particles), DMA (plates) and DMF recrystallized products (plates).

2.2.2. Powder X-Ray Diffraction (PXRD)

The X-ray diffraction pattern of a solid-form is characteristic of its polymorphic form and is a sensitive tool for determining the crystallinity of a material, as it gives direct information about the molecular arrangement within the crystal (Chao and Vail 1987). All recrystallized products showed sharp diffraction peaks, thereby confirming their crystalline (polymorphic/solvate) nature. The pattern

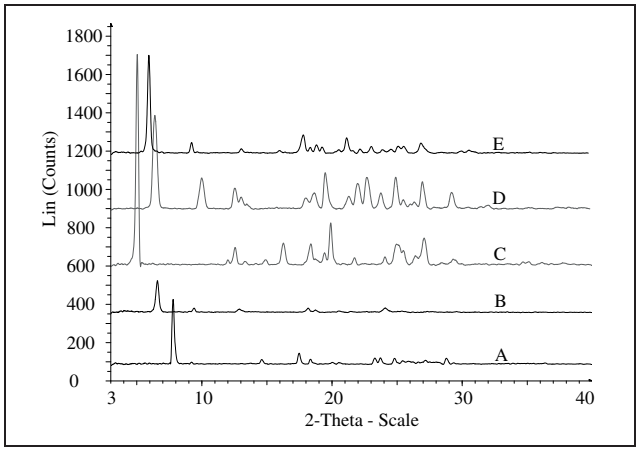

Fig. 2: PXRD patterns of products recrystallized from, (A) acetic acid : methanol (1 : 1), (B) ethyl acetate, (C) methanol, (D) DMA and (E) DMF

of as received sample matched with that of reported pattern of form C, which owing to its better solubility than form A is the pharmaceutically useful form, although form A has been reported to be the most stable one (Costa et al. 1991).

The crystals generated using a mixture of acetic acid : methanol (1 : 1) showed peaks corresponding to form A, while those generated in the presence of ethyl acetate and methanol depicted patterns similar to form B and C, respectively (Fig. 2). Also, the PXRD patterns of products recrystallized from DMF (hereafter mentioned as MBZ-DMF) and DMA (hereafter mentioned as MBZ-DMA), were distinctly different from any of the reported forms of MBZ, thus suggesting modification in the arrangement of molecules within the crystal lattice. This could be attributed to the formation of a new polymorph or solvate form of MBZ.

2.2.3. Thermal methods

Thermal methods can be used to clearly distinguish between polymorphs and solvates by the event of desolva-

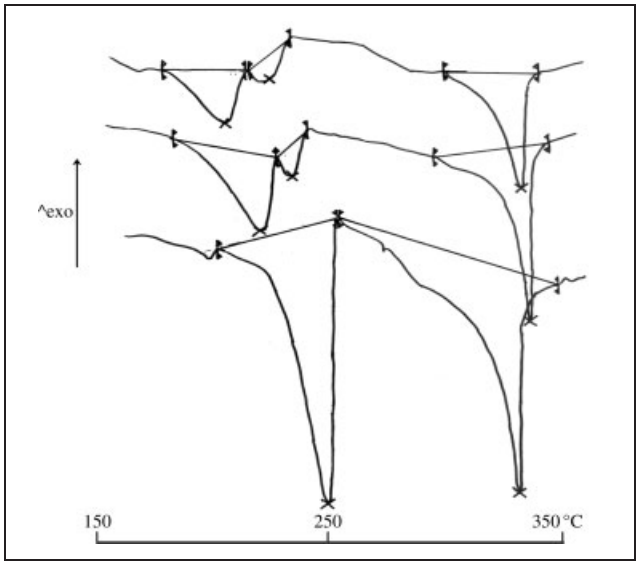

Fig. 3: DSC thermograms at 10 °C/min of products recrystallized from methanol; ethyl acetate and aceic acid : methanol (1 : 1) mixture (arranged from top to bottom)

tion in the latter. Crystalline MBZ and solvent recrystallized products were initially characterized by DSC and TGA at heating rates of 2.5 and 10 °C/min. DSC analysis of both the as received sample of MBZ and methanol recrystallized product showed three endothermic peaks at 208, 233 and 315 °C, corresponding closely to the thermal events of form C. The initial small endotherm at 208 °C is followed by the recrystallization of form C to A, hence the latter two endotherms correspond to the higher melting form A (Swanepoel et al. 2003).

Solvent recrystallized products showed different endothermic peaks in DSC (Fig. 3), further confirming the alteration of the solid state during recrystallization. MBZ recrystallized from a mixture of acetic acid : methanol showed endotherms at 250 and 322 °C, corresponding to form A of MBZ; while ethyl acetate recrystallized product showed peaks at 228, 241 and 329 °C, similar to form B. MBZ-DMA and MBZ-DMF showed a shift of endothermic peaks to lower temperatures and absence of peaks in the range mentioned for form C, indicating the possibility of new polymorph and/or solvate formation. Heating rate has a strong influence on the kinetics and resolution of two peaks (Giron 1995), which was also seen in case of MBZ-DMA and MBZ-DMF. At 10 °C/min, MBZ-DMA exhibited a broad endothermic dip at 180 °C followed by two endothermic peaks at 224 °C and 322 °C (Fig. 4a). On the other hand, at 2.5 °C/min three endothermic peaks at 183, 231 and 306 °C were observed. Similarly, in case of MBZ-DMF (Fig. 4b), the shoulder in peak observed at 10 °C/min at 225 °C resolved at a slower heating rate of 2.5 °C/min into two separate endotherms.

Hot stage microscopy was done to visually observe the events occurring in DSC. In case of form C (as received drug and methanol recrystallized product), a polymorphic transformation to form A was seen (Fig. 5). Form C showed melting and recrystallization to larger needles of form A at 213–225 °C, which finally melt with degradation at 327 °C. In all cases the values closely resembled the temperature of endothermic peaks in DSC. MBZ-DMA and MBZ-DMF, when observed by oil immersion method, exhibited release of bubbles (between 210–240 °C in MBZ-DMA and 180–250 °C in MBZ-DMF) from within the crystal lattice (Fig. 6), which is characteristic of solvates. The corresponding endothermic peaks in DSC at 183 and 213 °C in MBZ-DMA and MBZ-DMF, respectively, thus can be ascribed to desolvation. Desolvation was followed by melting at a temperature of 322 °C corresponding to the higher melting form A. Desolvation upon heating involves initial molecular loosening at the solvent sites, crystal darkening and generation of diffusion paths for escape of solvent molecules. The thermal events were thus clearly observed under HSM and correspond well to the endotherms in DSC. The comparative analysis of these solid-state forms using the available analytical tools has been presented in Table 2.

These solvent recrystallized products were also characterized by TGA to further assess solvate formation. Although, MBZ-DMA and MBZ-DMF exhibited weight loss of 20.80% and 25.53%, respectively, the exact stoichiometric amount present in the crystals could not be determined because pure MBZ also showed considerable weight loss with temperature, owing to the formation of degradation

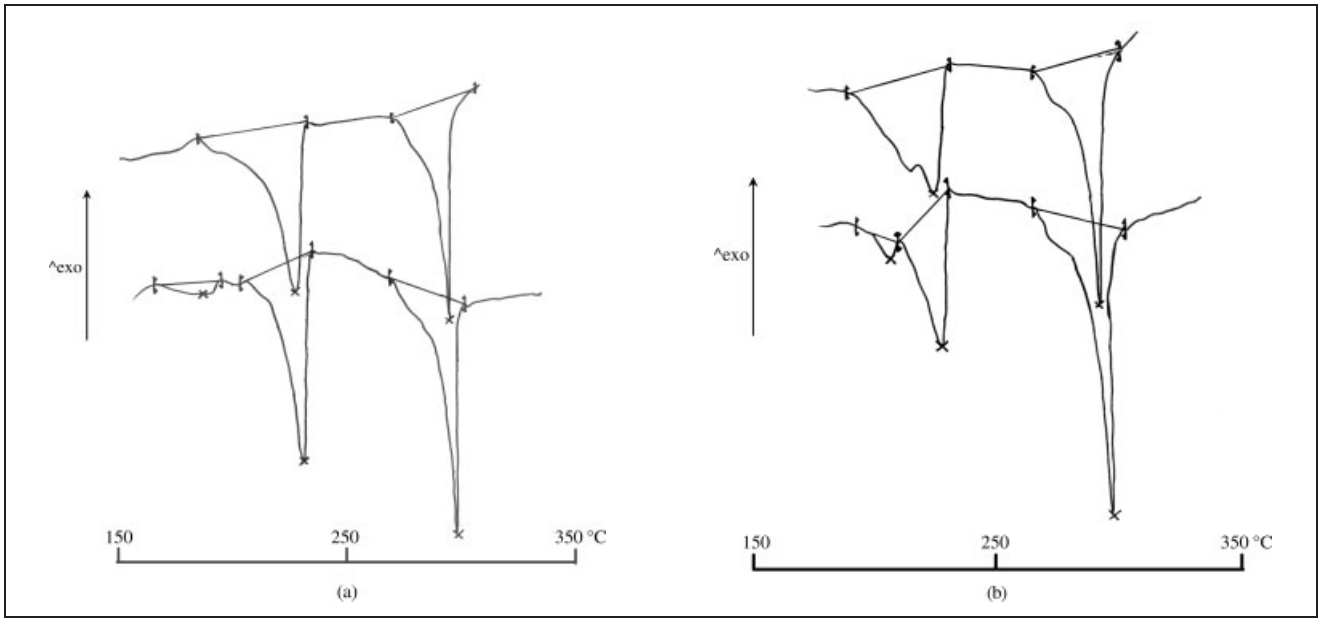

Fig. 4: DSC thermograms of (a) MBZ-DMA and (b) MBZ-DMF at different heating rates (up-curve) at 10 °C/min and (downcurve) at 2.5 °C/min

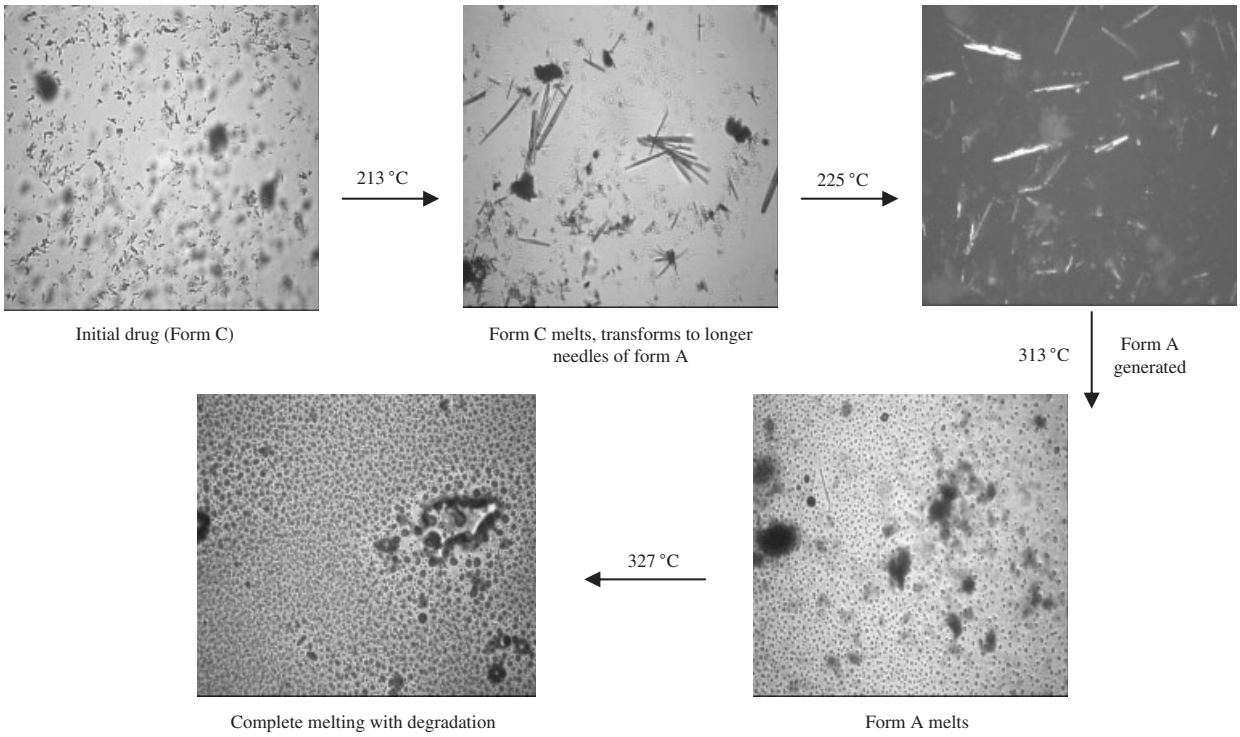

Fig. 5: Polymorphic transformation in form C of MBZ, as viewed under hot stage microscope at 500x

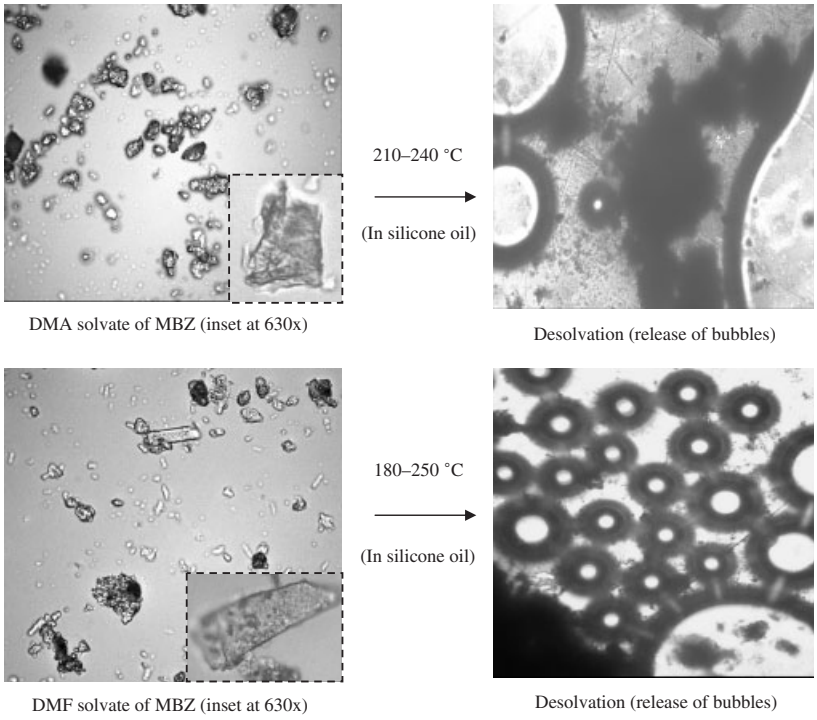

Fig. 6:
Photomicrographs of MBZ solvates at 500X (a) DMA solvates, (b) DMF solvates, as viewed under hot stage microscope

Table 2: Solid-state forms of MBZ characterized using various analytical tools

Solvent	Polymorphic form	Microscopic observation	DSC
Acetic acid : methanol (1 : 1)	Form A	Needles	Endothermic peaks at 255 and 326 °C
Ethyl acetate	Form B	Irregular particles	Endothermic peaks at 235, 246 and 332 °C
Methanol	Form C	Needles	Endothermic peaks at 223, 238 and 327 °C
DMA	Solvate of MBZ	Plates HSM: release of bubbles at 210–240 °C	Desolvation peak at 183 °C, followed by two melting endotherms at 231 and 306 °C
DMF	Solvate	Plates HSM: release of bubbles at 180–250 °C	Desolvation peak at 213 °C, followed by two melting endotherms at 235 and 307 °C

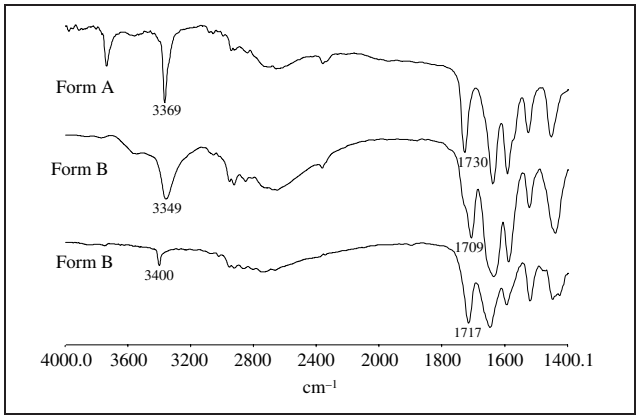

Fig. 7: FTIR spectra of three polymorphic forms of MBZ

products. It has been previously reported that major decomposition products are formed when MBZ was heated to 235 °C (which interferes with the desolvation temperature of solvates). These degradation products were identified by mass spectroscopy as 2-amino-5-benzoyl-(1*H*)-benzimidazole, 2-isocyanato-5-benzoyl-(1*H*)-benzimidazole and 1-methyl-2-amino-5-benzoyl-(1*H*)-benzimidazole (Costa et al. 1991). Also, owing to the poor nature of crystallization of MBZ, single crystal data for this drug is not available.

2.2.4. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different solid-state forms of an organic compound (Brittain 1997). Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies, leading to frequency shifts and splitting in absorption bands. The FTIR spectra of MBZ shows characteristic −C=O and −N−H stretching at 1717 and 3400 cm^{-1}, respectively (Swanepoel et al. 2003). The three polymorphic forms exhibited unique peaks in the FTIR spectra also (Fig. 7). The characteristic bands for −C=O stretching were seen at 1730 and 1709 cm^{-1} in form A and B, respectively, while −N−H band was observed at 3369 cm^{-1} for the former and 3349 cm^{-1} for the latter. The −C=O stretching band observed at 1664 cm^{-1} for DMA shifted to lower frequency of 1651 cm^{-1} (Fig. 8a) in the case of solvate. In case of MBZ-DMF, clear shift in bands could not be observed by just analyzing the solvent and solvate spectra. Hence, the spectrum subtraction option available in the software was used to deduct the spectrum of MBZ from that of the solvate to observe any changes in the peaks remaining due to the solvent (DMF). It was found that the −C=O stretching band at 1664 cm^{-1} in pure DMF shifted to a lower value of 1614 cm^{-1} in the 'difference spectrum' of solvate and the drug (Fig. 8b). Lowering of frequencies was also seen for −N−H stretching bands from 3402 to 3353 cm^{-1} in MBZ-DMA (Fig. 8c), and from 3402 to 3372 cm^{-1} in MBZ-DMF (Fig. 8d), as compared to pure drug. These shifts in frequencies indicate the possibility of hydrogen bonding between the –C=O group of solvents and the −NH groups present in MBZ. The hydrogen bonding may lead to an increase in negative charge over oxygen atom due to the shift of π electrons of −C=O group, thus, resulting in the weakening of its double bond character and a red shift.

2.3. Solubility determination of solvates

Solubility determination is of vital importance for pharmaceutical compounds, especially in the case of poorly solu-

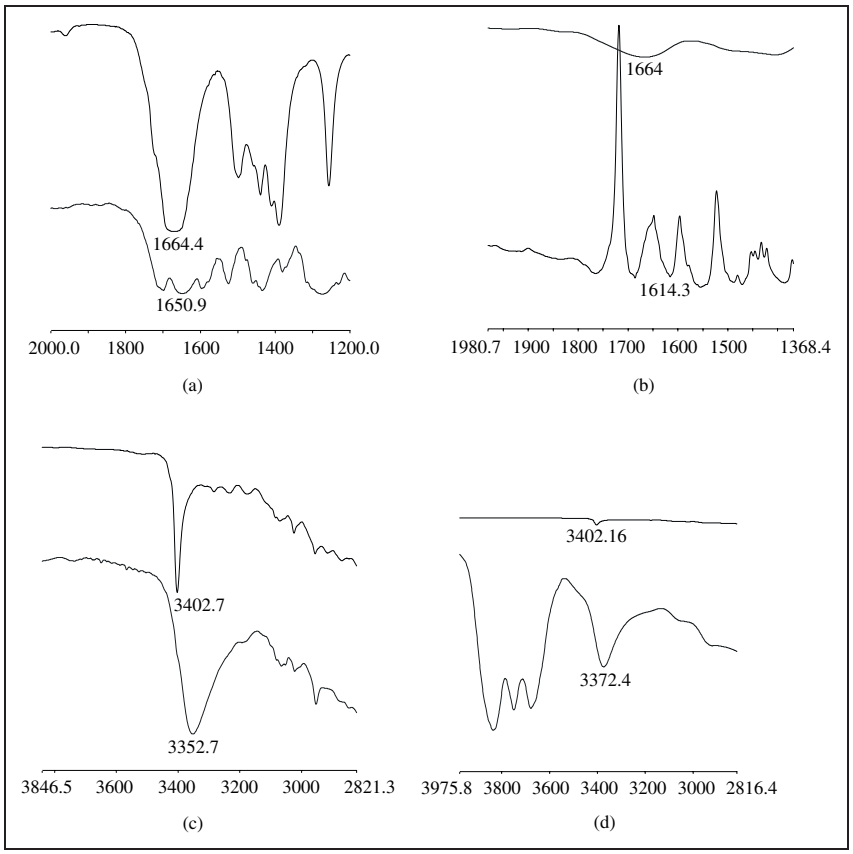

Fig. 8:
FTIR spectra of MBZ solvates (a) −C=O peak shifts in DMA (top) and MBZ-DMA (bottom) and (b) DMF (top) and the difference spectra of the solvate and drug (bottom); (c) −N−H peak shifts in MBZ (top) and MBZ-DMA (bottom), (d) MBZ (top) and MBZ-DMF (bottom)

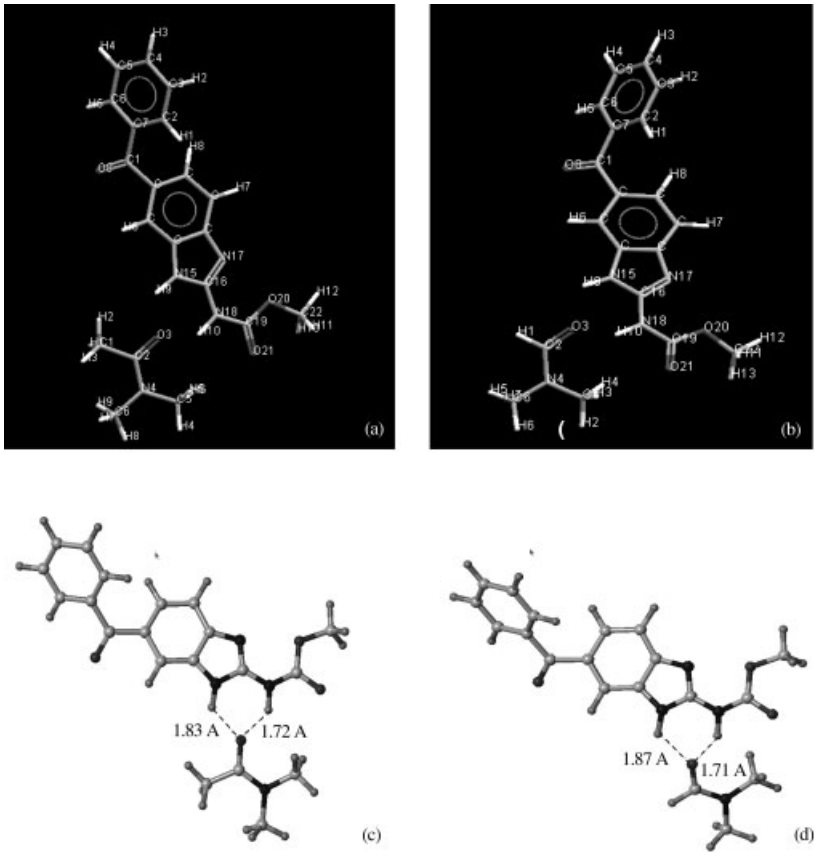

Fig. 9:
Molecules showing the hydrogen bonding and bond distances (a) docking of DMA with MBZ molecule, (b) docking of DMF with MBZ molecule, (c) MBZ-DMA hydrogen bonding, (d) MBZ-DMF hydrogen bonding between H_9-O_3 and $H_{10}-O_3$

ble drugs. Since different crystal structures are characterized by different lattice energies (and enthalpies), it follows that the solubility of different crystal polymorphs (or solvates) must differ as well (VanTonder et al. 2004). Solvates usually show a higher solubility than the non-solvated form, because inclusion of organic solvents in the solvated form has been reported to weaken the crystalline lattice (Brittain and Grant 1999). MBZ-DMA and MBZ-DMF gave a higher peak solubility value of 5.82 ± 0.01 μg/ml, and 4.86 ± 0.04 μg/ml, respectively, as compared to 3.16 ± 0.03 μg/ml for MBZ. On statistical evaluation of results using one-way ANOVA, the difference in the mean values between groups was greater than would be expected by chance, hence, there is a statistically significant difference ($p < 0.001$) between the solubility values of solvates and the non-solvated form C.

Solvates have been reported to undergo solution mediated transformation and have also been found to exhibit a fall in solubility after attaining the peak value (Chawla et al. 2003). The DMA and DMF solvates of MBZ did not show such a behavior. No solution mediated transformation was observed in water even after a period of 24 h, when viewed under microscope, thereby suggesting their relatively stable nature compared to most known solvates.

2.4. Molecular modeling studies

Molecular modeling has a diverse range of applications varying from building and visualizing molecules to performing complex calculations on molecular systems. The calculations carried out using Sybyl® 7.1 helped in docking the drug and the solvent molecules together after energy minimization. The stable structures obtained after minimization were analyzed for the putative hydrogen bonding interactions between the drug and the solvent molecules. The study confirmed the hydrogen bonding between −N−H groups of MBZ and −C=O group of solvents as observed by the shift in FTIR vibrational peaks of MBZ-DMA and MBZ-DMF. Figure 9 shows the molecular structures of the drug and the solvents (DMA and DMF) when docked using the option available in Sybyl®. The probable sites for hydrogen bonding are H_9 and H_{10} of MBZ with O_3 of the solvents. The hydrogen bond distances were calculated in these solvated systems as MBZ-DMA: N−H···O 1.83 Å and 1.72 Å; and MBZ-DMF: N−H···O 1.87 Å and 1.71 Å. Hydrogen bonds have been classified according to their strengths by Jeffrey (1997) whereby a moderate H-bond has a H...Y distance of ∼1.5–2.2 Å and a X−H...Y distance of ∼2.5–3.2 Å and weak H-bonds have a corresponding value of ∼2.2–3.2 Å and ∼3.2–4.0 Å, respectively. According to this classification, the H-bonds present in these solvates are moderately strong.

Hydrogen bond patterns can be described and compared using the Graph Set Notation (Etter et al. 1990). Graph sets describe the topological nature of H-bond pattern and the number of donors and acceptors involved. A graph set is specified as represented below (Adsmond and Grant 2001, Bernstein et al. 1995)

$$G_d^a(r) \qquad (1)$$

where G is the pattern designator, a and d are the number of acceptors and donors, r is the total number of atoms involved in the pattern.

Pattern designator (G) describes the pattern of H-bonding and can be one of the four types: S (self/intramolecular bonding), C (chain), R (ring), D (other finite pattern). The DMA and DMF solvates of MBZ can both be represented by the graph set $R_2(6)$, where C_{16}, N_{15}, N_{18}, H_9, H_{10} of MBZ and O_3 of solvent form the ring structure. The hydrogen atoms (H_9, H_{10}) attached to nitrogen in the drug act as the hydrogen bond donors while the oxygen (O_3) of

the solvent is the acceptor. Both the solvates showed a similar pattern of bonding due to the similarity in their structures.

2.5. Conclusion

Solvent recrystallization led to the generation of alternate solid-state forms of MBZ. Apart from the three reported polymorphic forms A, B and C, two new solvates of MBZ were generated using DMA and DMF. The desolvation events observed in HSM confirmed the presence of solvent molecules within the crystal lattice. These plate shaped solvates exhibited a higher solubility in comparison to the non-solvated needle shaped form C. Moreover, these solvates did not exhibit any solution mediated transformation as reported for most of the pharmaceutical solvates. Both DMA and DMF, due to their propensity to interact with the solute molecules, formed moderately strong hydrogen bonds with MBZ. FTIR and molecular modeling studies further confirmed the bonding pattern between the solvent and drug molecules.

3. Experimental

3.1. Materials

Crystalline MBZ was gifted by Supharma Chem, Gujarat, India. All other reagents used were either HPLC or AR grade.

3.2. Solubility determination of drug in solvents

Saturation solubility of MBZ in different solvents (Table 1) was determined by the 'synthetic method' wherein actual analysis of solution is not carried out. A weighed amount of drug was placed in 5 ml screw capped glass vials to which incremental addition of solvent was carried out until the solution remained clear. The approximate visual solubility of the drug in solvents was determined by noting the amount of solvent required to completely dissolve the known weight of drug.

3.3. Preparation of solid-state forms

The solvent recrystallization approach was used for polymorph screening using solvents based on solubility studies. Supersaturated solution of the drug was prepared by dissolving its excess amount in the solvent at 60 °C, and the filtered solution was stored at room temperature to allow crystallization. In case of high boiling solvents, like DMA and DMF, the solution was evaporated under reduced pressure using a rotavapor (R-200 Buchi Labortechnik AG, Switzerland). The crystals were collected and dried at 25–30 °C.

3.4. Characterization

3.4.1. Microscopy

Crystal habit was observed at different magnifications both with and without silicone oil, under optical and polarized light using Leica DMLP polarized light microscope (Leica, Wetzlar, Germany) equipped with IM 50 V1.20 Twain module imaging software (Leica, Germany).

3.4.2. Powder X-ray Diffraction (PXRD)

PXRD patterns of the solid forms were recorded at room temperature on Bruker's D8 Advance diffractometer (Karlsruhe, Germany) CuKα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter with divergence slit (0.5°), antiscattering slit (0.5°), and receiving slit (1 mm). The diffractometer was equipped with a 2θ compensating slit, and was calibrated for accuracy of peak positions with silicon pellet. Samples were subjected to X-ray powder diffraction analysis in continuous mode with a step size of 0.01° and step time of 0.5 sec over an angular range of 3 to 40° 2θ. The recrystallized products were loaded in a poly methyl methacrylate (PMMA) holder and pressed by a clean glass slide to ensure coplanarity of the powder surface with the surface of the holder. Obtained diffractograms were analyzed with DIFFRAC plus EVA (ver. 9.0) diffraction software.

3.4.3. Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Mettler Toledo 821^e DSC (Mettler Toledo, Switzerland) operating with Star^e software version Solaris 5.1. Temperature axis and cell constant were calibrated using indium and zinc. The samples were exposed to heating rates of 2.5 and 10 °C/min over a temperature range of 25–350 °C under nitrogen purging (80 ml/min) in pinholed aluminium pans.

3.4.4. Thermogravimetric analysis (TGA)

TGA was performed using Mettler Toledo 851^e TGA/SDTA in alumina crucibles at a heating rate of 10 °C/min from 25 to 350 °C under nitrogen purging (20 ml/min).

3.4.5. Hot stage microscopy (HSM)

HSM was carried out using Leica DMLP polarized light microscope and Leica LMV hot stage. Photographs were taken using Leica DC 300 camera. Samples were mounted with or without silicone oil, and heated from 25 to 350 °C.

3.4.6. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of the samples were obtained on a Perkin-Elmer spectrophotometer (Perkin-Elmer Corp., UK) equipped with Multi-scope analyzing software, by the conventional KBr pellet method. Liquid samples were taken neat on KBr discs. The spectrum for each sample (an average of 16 co-added scans) was recorded over the 450 to 4000 cm^{-1} spectral region with a resolution of 4 cm^{-1}.

3.5. Solubility determination of solvates

Solubility was determined by placing an excess amount of sample in 5 ml of water (maintained at 37 °C) in screw-capped glass vials, in shaker water bath (Julabo Labortechnik GmbH, Seelbach, Germany) at 200 rpm. Samples were withdrawn at regular intervals, filtered, and analyzed after appropriate dilution using UV spectrophotometer at a wavelength of 245 nm.

3.6. Molecular modeling of solvates

Molecular modeling studies were carried out using a previously reported method (Gandhi et al. 2002) with Sybyl® 7.1 software installed on Silicon Graphics Fuel Workstation. The molecules were built using sketch option available in Sybyl®. The molecules were individually minimized using Powell's conjugate gradient method with Tripos force field and Gasteiger-Huckel partial atomic charges. The minimum energy difference of 0.05 kcal/mol was set as the convergence criterion. The solvent molecules DMA and DMF were manually docked into the drug MBZ in 3D using the molecular graphics tools available in Sybyl®. After docking the solvents, the drug-solvent complexes were subjected to full minimization to find out the probable hydrogen binding sites. The stable structures obtained after minimization were analyzed for the putative hydrogen bonding interactions between the drug and the solvent molecules.

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