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New co-crystal and salt form of sulfathiazole with carboxylic acid and amide

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Abstract.

One co-crystal and one salt of an antibacterial drug malfathiazole with 4-aminobenzamide and 24 dimitrobenzoic acid have been synthesized. These new forms are characterized by single crystal X-ray diffraction, infrared spectroscopy, differential scanning calorimetry (DSC) and thermogravimetricanalys (TGA) In solid state, sulfathiazole preferentially adopts the imidinetautomeric form

Keywords Co-crystal pharmaceutical, salt; tautomerism, valfathianule, sythen

1. Introduction

Crystal engineering is defined as the understanding efimermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties In recent times this approach has been down to be very useful for obtaining co-crystal and salt forms of active pharmaceutical ingredients (APIs) with improved physicochemical properties compared to the original APIs, without affecting the pharmacologi. calbehaviour In this regard, supramolecularsynthon approach is very useful as it provides the basis for selec 22 tion of co-formers. Hence it is important to under stand the role of competing functional groups and their preference for forming supramolecularsynthons in a complex crystalline environment. In this context, sulfa drags, such as sulfathiazole, sulfamethazine, etc. with high conformational flexibility have always been attrac the, as they possess several strong hydrogen bonding groups such as S*O_{2} NH and N*H_{2} The ar tic groups on the drug molecules also play a key le by forming -stacking interactions with aromatic co-former and thus promote the formation of molecular complexes, such as co-crystals, salts, solvates, etc

Sulfathiazole (STZ) is a short acting sulfa drug and has a spectrum of antimicrobial actions. It has two types of suong donors (amine N*H_{2} and a sulfonamide NH) with a total of three acidic protons. There are two types of soning acceptors, two sulfoxy O-atoms, one amine N- zom. Here we present two new multicomponent forms

For corespondence

of STZ, namely a co-crystal with 4-aminobenxamide (4AMB), and a salt with 2,4-dinitrobenzoic acid (DNB)

2. Experimental

21 Materials

Sulfathiazole drug, the co-crystal former and salt for mer were purchased from Sigma-Aldrich Commercially available solvents were used without further purification

Sople crystal preparation

Sulfathiazole drug and co-former in a 1:1 stoichiometric ratio was taken in a 10mL conical flask followed by addition of ethanol. The suspension was heated until a clear solution was obtained. The solution was left for slow evaporation at ambient condition. Single crystals suitable for X-ray diffraction studies were obtained in approximately 5-7 days.

2.3 Crystallography

Co-crystal and salt of sulfathiazole were individually mounted on a glass pipe Intensity data were col- lected on an Agilent SuperNova system with graphite monochromatic Mo Ko radiation at 100 K. Data reduction was done using CrysAlisPro software. Crystal structures were solved by direct method using SHELXL-97 and refined by full matrix least square on p with anisotropic displacement parameters for all non H atoms using SHELXL-97.

24 Differential scanning calorimetry (DSC)

DSC was performed on a Mettler Toledo DS11 STAR instrument. Accurately weighed samples (2-3 mg) were placed in hermetically sealed aluminum crucibles (40 uLs with a pin hole on lid, and scanned from 30 to 300 C at a beating rate of 5°C/min under a dry nitrogen atmosphere

25 Thermogravimetric analysis (TGA)

TGA was done on a Mettler Toledo TGA/SDTA B5 instrument. Approximately (5-6 mg) of the sample was added to an aluminum crucible and heated from 30 to 300 C at a rate of 10°C/min under continuous nitrogen purge

2.6 IR spectroscopy

Transmission infrared spectra of the solids were obtained using a Fourier transform infrared spectrometer KB samples (2 mg in 20mg of KB) were pre pared and 10 scans were collected at 4c * m ^ - 1 resolution for each sample Spectra were measured over a range of 4000-400 cm

3. Results and Discussion

31 Sulfathiazole/24-dinitrobenzoic acid (1.2) salt (STZ/DNB)

The salt, STZ/DNB, crystallizes in the triclinic P-1 space group with one molecule of STZ and two molecules of DNB in the asymmetric unit. Here the sulfathiazole molecule, which adopts a V-shape conformation, exists in midinetautomeric form due to the transfer of proton from sulfonamide NH to thiazole ring N-atom (scheme 1). On the other hand, the intermolecular pro ton transfer from carboxylic acid group of one DNB molecule to the N*H_{2} group of the STZ molecule leads to the formation of the salt. It is generally suggested that a minimum of 3 pKa difference (Apkaj between API and co former (acid-base pair) is required for an assured salt formation, while a co-crystal is formed when the triangle pKa< 0 and either a co-crystal or salt form may result when the Apka is between 0 and 3. Hence, here as the ApKa between STZ * (nKa = 72) ^ 2 and DNB (pKa =1 43)^ 9 is 577, the formation of salt instead of the neutral co-crystal form is not surprising

In the structure, a trimer is formed, via cyclic synthon 1 (N(13) H(13) O(30), d/A 0 191 A 175), N(11)-

H(11B) 0(31), 178(3) A. 172(3)) N(11) H(11A) N(10),2.04(3) A. 179(4)"), by involving the

Symbol

Figure 1. Crystal packing in sulfathiazole/2,4-dinitrobenzoic acid (12) sait (STZ/DNB). (a) Formation of a trimersynthon 1 by two STZ and one DNB molecules, and synthon 2 between NH, and Osy groups. (b) Formation of 1D tapes by STZ molecules via syn- thon I and synthon 2 (the co-former, DNB, molecules are not shown for clarity) (c) Crystal structure viewed along a-axis to show the packing of co-former molecules with respect to the parallel ID tapes.

Formation of new solid forms is studied by infrared spectroscopy Comparison of spectra of the pure in- tial co-formers and the new forms clearly demonstrate the peak shift for major peaks, such as - N * H_{2}, - C = O etc., peaks of acid and amide groups in the co-former (figures S1 and S2)

3.4 Thermal Analysis

To study the thermal behaviour of the new forms with of respect to API, DSC and TGA, experiments were car ried out, which are presented in figure 3. DSC moni- tors heat flow, associated with the effect of phase tran- pref-sition and chemical reactions as a function of temper ature. The melting transition temperatures of the co- crystal and salt forms were distinct from either of the individual components confirming the formation of new phases. The DSC thermogram of STZ/4ABM co-crea showed a single, melting endotherm at 190°C, while the

As the STZ molecules in both the salt and co-crystal ded here, exist in the imidinetautomeric form camed out a Cambridge Crystallographic Database CSD version 5.35) search to examine the tautomerism the earlier reported structures. A search with filters: 3D coordinates determined, 2) R factor <= 0.075 .disordered and 4) no errors found 30 STZ structures. Notably in all the cases, the STZ wecule existed in imidinetautomeric form, but never ce of STZ drug for the imidinetautomeric form. form. Hence this suggests a strong ke earlier study, we reported such a preference mylsulfathiazole, which also showed a strong 10 for the de structures.

ambon 4 (N(3)-H(8B) O(1).2.47A 162"); N(3)- 838) 0(1): 214(3) A. 149(3)") that leads to the on of 2D sheets with a parquet floor network, as in figure 2b. The 2D sheets are further connected N-HO hydrogen bonds extending the network ate third dimension.

3.3 Infrared spectroscopy

New co-crymal and salt of sulfathiazole

present, the TGA curves of both the co-crystal and salt and salt (STZ/DNB) are provided in the supplementary dowed single weight loss peaks, corresponding to the information. Amposition (higureSc, di

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Supplementary Information

In spectra, ORTEP representation, crystallops- acture refinement parimmers and bydro-11 Enter MC and Macdonald JC 1990 ActaCrystalloge B bind piameter of STZ co-crystal (STZ4ABM)

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4 Conclusion

Ohe new co-crystal and one salt form of sulfathia ole drug with a carboxylic acid and amide are syn Bound and characterized by single crystal XRD, DSC, TGA and infrared spectroscopy Crystal struc analysis revealed that the strong hydrogen bond- groups, amely carboxylate (in STZ/DNB salt) and amde group in STZAABM) interact with the song midine cine. The second strongest groups, SO, and NH, from STZ and/or co-former, imteract to form 4.Adinceddogen bonds. This is consistent with the fact that the sing acceptors prefer ng donors and weak aponspreler weak donors." The present and the ported in CSD reveal the strong prefer- Gwth Des 14 803 mor of STZ molecule to exist in imid