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Structural and physicochemical characterization of pyridine derivative salts of anti-inflammatory drugs

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ABSTRACT

Salts of common anti-inflammatory drugs mefenamic acid (MFA), tolfenamic acid (TFA) and naproxen (NPX) with various pyridine derivatives (4-amino pyridine (4AP), 4-dimethylaminopyridine (DMAP) and 2-amino pyridine (2AP)) were synthesized by crystal engineering approach based on the pK_a values of API's and the salt former. All the salts were characterized systematically by various spectroscopic methods including FT-IR and ^1H NMR and the crystal structure was determined by single-crystal X-ray diffraction techniques (SCXRD). DMAP salt of NPX and 2AP salts of MFA and TFA were not obtained in the salt screening experiments. All the molecular salts exhibited 1:1 molecular stoichiometry in the asymmetric unit and except NPX-2AP salt, all the molecular salts included a water molecule in the crystal lattice. Physicochemical and structural properties between drug-drug molecular salts of MFA-4AP, TFA-4AP and NPX-4AP have been evaluated and it was found that these molecular salts were found to be stable for a time period of six months at ambient condition and further hydration of molecular salts were not observed even at accelerated humid conditions (~75% RH). It was found that 4AP salts of MFA and TFA and DMAP salts of MFA and TFA are isostructural.

1. Introduction

The term Crystal Engineering was introduced first by the scientist Ray Pepinsky and defined it as "crystallization of organic ions with a metal containing organic metal ions of suitable sizes, charges and solubilities yielded structures with cells and symmetries determined mainly by packing of complex ions [1,2]." Crystal engineering approach is based on the utilization of intermolecular interactions, thereby design the functional molecules with targeted properties. Recently the field of crystal engineering has gained greater importance in the field of the pharmaceutical industry due to its utility for the modification of active drug ingredients without affecting the biological activity by co-crystallization techniques [3]. Co-crystallization approach brings modification of physicochemical properties of drug molecule such as solubility, stability, compressibility and hygroscopicity. The advantages of salts/co-crystal for improving the physical property is that the structure of the molecule remains unchanged, however, the modification is at the supramolecular level by exploiting intermolecular interactions and crystal packing [4–6]. Salt formation (100–1000 times) is the most preferable for solubility enhancement of drug molecule when compared to co-crystal (4–20 times) and polymorphs (2–3 times) [7–9]. However, the disadvantage is that salts are more susceptible to form hydrates when compared to co-crystals. Over 50% of commercial drugs in the market are salts. The formation of salt or co-crystal is generally predicted by the pK_a rule, where if the ΔpK_a (pK_a of the conjugate acid of base-pK_a of acid) value is less than 0 will give a neutral co-crystal. If the value is more than 3 then the complex preferably forms a salt and the range in between 0 and 3 is a salt/co-crystal continuum zone for molecules [10,11].

The three active pharmaceutical ingredients (API) chosen in the present study namely mefenamic acid (MFA), tolfenamic acid (TFA)

Abbreviations: API, active pharmaceutical ingredient; FDA, food and drug administration; BCS, biopharmaceutical classification system; MFA, mefenamic acid; TFA, tolfenamic acid; NPX, naproxen; 4AP, 4-aminopyridine; DMAP, 4-dimethylaminopyridine; 2AP, 2-aminopyridine; SCXRD, single crystal x-ray diffraction; PXRD, powder x-ray diffraction; FT-IR, fourier transform infrared; DSC, differential scanning calorimetry; NMR, nuclear magnetic resonance; RH, relative humidity.

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and naproxen (NPX) are non-steroidal anti-inflammatory drugs. All the APIs falls under the biopharmaceutical classification system (BCS) class II drug due to their poor aqueous solubility and high permeability. MFA and TFA are anthranilic acid derivatives used to treat mild to moderate pain and furthermore these drugs used to prevent migraines associated with menstruation [12,13]. NPX is a propionic acid class of drug used to treat fever, pain, swellings and stiffness [14]. Salt formers used in the study are pyridine derivative moieties namely 4-aminopyridine (4AP), 4-dimethylaminopyridine (DMAP) and 2-aminopyridine (2AP) (See Scheme 1). 4AP used in the present study as a salt former is a drug molecule used for the treatment of multiple sclerosis by blocking the potassium channel. This is the first drug that was specifically approved to help with mobility in multiple sclerosis patients and it is approved by U.S food and drug administration (FDA) in the year 2010 [15,16]. However, 2AP and DMAP are toxic materials and can't be used with drug substances.

Numerous reports are available in the literature on co-crystal/salts of naproxen API. However, a few co-crystal/salts are reported for MFA and TFA APIs. Reported co-crystals of MFA and TFA include nicotinamide [17] and 4, 4'-bipyridine [18]. A drug-drug cocrystal of MFA with paracetamol was reported by Chirag et al. in the year 2013 [19]. Dixit et al. prepared microparticle of MFA with β-cyclodextrin to enhance the solubility of MFA drug [20]. Co-crystals/salts of NPX include nicotinamide, isonicotinamide, picolinamide, bypyridine, piperazine, proline, S-arginine, L-alanine, D-alanine, D-tyrosine and D-tryptophan [21–29]. Therefore in the present study salt screening experiment was carried out with pyridyl derivative as the salt former based on the pK_a values of APIs and the salt former. Salt screening experiment resulted in two molecular salt hydrate of MFA with 4AP and DMAP, two molecular salt hydrate of TFA with 4AP and DMAP and two molecular salts of NPX with 4AP and 2AP, where NPX-4AP is a salt hydrate. However, DMAP salt of NPX and 2AP salt of MFA and TFA were not obtained in the salt screening experiment. The stability study associated with three of the drug-drug salts (MFA-4AP, TFA-4AP and NPX-4AP) were evaluated in the present study.

2. Materials and methods

Mefenamic acid, tolfenamic acid and naproxen APIs were purchased from TCI chemicals and used as such without any further purification. Salt formers 4-amino pyridine, 4-dimethylaminopyridine and 2-amino pyridine were purchased from various vendors and used as such. All the crystallization experiments were carried out using analytical grade solvents.

2.1. Synthesis of molecular salts

All the molecular salts synthesized in the present study followed solvent evaporation method and pure crystals were obtained in all the cases.

2.1.1. Solvent evaporation method

The equimolar ratio of API and the salt former were taken together in a 25 mL glass beaker, dissolved in a particular solvent of 10 mL (MFA-4AP: ethanol, MFA-DMAP: ethanol, TFA-4AP: methanol, TFA-DMAP: ethanol, NPX-4AP: methanol, NPX-2AP: ethanol) at 60 °C and left for slow evaporation at room temperature. Good quality crystals suitable for SCXRD analysis were obtained in all the six cases.

2.2. Single crystal X-ray diffraction (SCXRD)

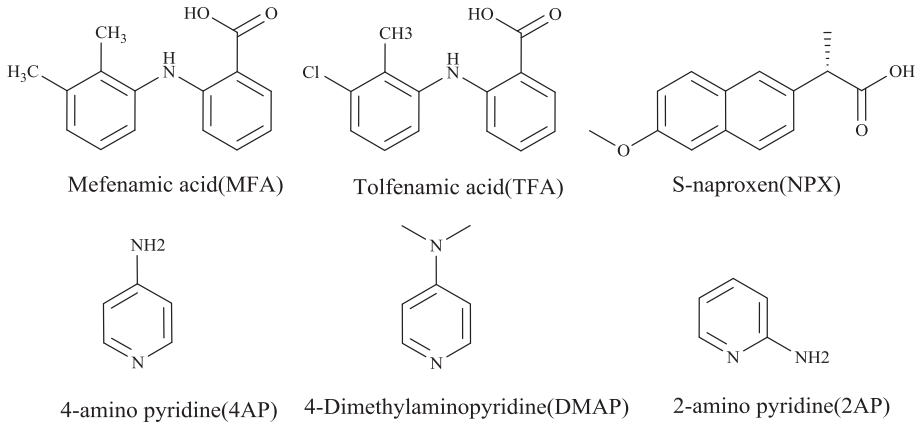
Single-crystal X-ray Diffraction data of synthesized molecular salts were collected on a Bruker Apex II duo diffractometer with dual system CCD detector. The Monochromatic Molybdenum (Mo) source was used with Kα radiation (λ = 0.7107 Å). For all the molecular salts, data collection was done at ambient conditions (296 K). Crystal structures were solved by SHELXL-2007/2014 software by direct methods and refinement was carried out by full-matrix least-squares technique [30]. H atoms attached to the N atoms were located in a difference Fourier density map and refined anisotropically.

2.3. Powder X-ray diffraction (PXRD)

Joel (JDX-8P) powder X-ray diffractometer instrument was used for the PXRD analysis with Cu Kα radiation of wavelength λ = 1.54059 Å. 40 KV and 30 mA voltage and the current were applied for the data acquisition. For the analysis, powdered samples were placed on a standard sample holder and scanned continuously from 5 to 50° with a scan rate of 2° min^{-1}.

2.4. ^1H NMR spectroscopy (NMR)

Bruker Biospin 400 MHz Spectrometer (Bruker, Germany) instrument was used for ^1H NMR analysis. ^1H NMR of all the molecular salts were recorded in a DMSO-d_6 solvent with TMS as the internal reference standard. Spectra was recorded with 16 number of scans.



Scheme 1. Molecular diagrams of APIs and the salt former.