# *Thesis Title: Preparation and Characterization of Various Solid Forms of Triamterene*

***By***

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## *Abstract*

The research in this thesis was aimed to prepare and characterize various solid forms of a drug 'triamterene' by salt formation, cocrystallization, amrophization and co-amorphization which could be used for pharmaceutical drug development. Triamterene was selected as an appropriate model compound because (i) it has poor water solubility (which can impact its bioavailability as a drug), (ii) it contains numerous hydrogen bonding sites, thereby allowing a study of the competition amongst the different potential synthons. This thesis provides a detailed discussion on the preparation and characterization of the products formed and stability under different conditions of temperature and relative humidity.

**Chapter 1** gives an overview of single component and multicomponent pharmaceutical solid forms and their solid state transformations including polymorphism. The strategies for the design, preparation and screening of the multicomponent solid forms are described. The coformers used with triamterene for salt formation/cocrystallization and co-amorphization are introduced. The experimental methods and characterization techniques used throughout this thesis are described in **Chapter 2**.

**Chapter 3** describes the salt solvates of triamterene with carboxylic and inorganic acids. Overall eight crystal forms are described in this Chapter. The coformers were selected based on the supramolecular synthon approach and *ΔpKa* rule was rationally adopted to get the desired crystal forms. Grinding and solution crystallization were used as crystallization techniques. The structure solution of all the crystal forms was obtained from single crystal X-ray diffraction (SCXRD) and further analyzed by TGA/DSC, hot stage microscopy and in one case by VTPXRD. In addition, desolvation of these crystal forms is extensively studied and considered it as a method to get anhydrous forms which are not achievable under ambient conditions. Solvent vapor absorption studies were also carried out to see the reversibility of desolvated adducts to the solvated forms.

In **Chapter 4**, seven crystal forms of triamterene with carboxylic, inorganic acids, Generally Regarded as Safe (*GRAS*) chemicals and other APIs are described. These crystal

forms either exist as anhydrous, hydrated or solvated salt forms. Further more, two of them exhibited rarely occurring solid state forms i.e. salt-cocrystal continuum and hybrid salt-cocrystal. All the structure solutions were attained by SCXRD except one (hybrid salt-cocrystal of triamterene with glutaric acid) where powder X-ray solution was utilized. The existence of different solid forms were further investigated by a combination of solid-state Fourier Transform Infrared (ssFT-IR), C-13 and N-15 Nuclear Magnetic Resonance Spectroscopy (ssNMR). Desolvation of the adducts studied in detail, resulted in several new anhydrous forms which need further experimental and computational work for characterization especially for structural elucidation.

The results presented in **Chapter 5** correspond to the formation of six anhydrous polymorphic, two hydrated and two solvated cocrystal forms between triamterene and theophylline. Initially cocrytal formation was achieved by the LAG and solution crystallization experiments utilizing LAG products, produced crystals which were confirmed as solvated cocrystals by SCXRD. Later on desolvation experiments using different heat treatments resulted in a series of polymorphic anhydrous forms. Four are studied in detail. Upon exposure to high relative humidity, form I and II converted to the hydrated forms. The structure solution of the two solvated forms were carried out by the SCXRD and for one anhydrous and one hydrated form by the X-ray powder solution and for others solutions from synchrotron data is in process. The competitive slurry data along with the thermal and ssFT-IR analysis supported the existence of monotropic relationship between the polymorphic forms.

**Chapter 6** describes three solvates and a hydrate of triamterene. All of them except one were obtained serendipitously as a result of unsucceful solution crystallizations between triamterene and coformers and demonstrates the ability of triamterene to readily produce different supramolecular architectures.

**Chapter 7** is of fundamental importance and gives a comprehensive account on the presence of all the hydrogen-bonded motifs between triamterene molecules, triamterene and coformers and triamterene and solvent molecules. Throughout the discussion of the crystal structures which were obtained, it was recognized that the standard graph set notation would not be sufficient to accurately describe the actual interactions since various ways of forming the same graph set could be envisaged. As a result the approach of a motif description was developed and utilized.

In **Chapter 8**, the amorphization of triamterene along with co-amorphization with glutaric, sebacic acids and theophylline is described. The neat grinding at room temperature, cryogenic temperature and melt quenching were used as amorphization techniques. Almost all the products were found to be X-ray amorphous. Assessment of the stability of the amorphous and co-amorphous materials at low and high relative humidities under different temperature

conditions showed the crystallization to the anhydrous salts/ocrystals and the hydrated forms. Extraordinary stability of the co-amorphous form of triamterene with theophylline (produced by the cryogenic temperature neat grinding and melt quenching) over several months recommends its usage in the pharmaceutical drug dosage forms.

**Chapter 9** presents an overall discussion and the concluding remarks with the emphasis on the achievement of goals set for the present research work and describes an overall summary of the outcomes of the work produced in thesis.