Synopsis

The thesis entitled “Exploring Intermolecular Space by Charge Density Analysis in Molecular Crystals” consists of five chapters. A short introductory note highlights the importance of intermolecular interactions and presents the current status of charge density analysis to obtain insights into such interactions. Charge density analysis of crystalline materials by using high resolution X-ray diffraction data has become routine and enables derivation of reliable one electron properties associated with the electron density. The results obtained from single crystal X-ray diffraction data at low temperature have been compared with periodic theoretical calculations using B3LYP/6-31G** methods to unequivocally establish the nature of weak interactions.

Chapter 1 describes the quantitative analysis of Cl···Cl intermolecular interactions in compounds 2-chloro-3-quinolinyl methanol, 2-chloro-3-hydroxypyridine and 2-chloro-3-chloromethyl-8-methylquinoline, which are corresponding to type I (trans and cis) and type II (L) geometries of Cl···Cl interactions respectively. The 3D static deformation density plots from charge density analysis unequivocally suggest that both ‘cis’ and ‘trans’ type I geometries show decreased repulsion whereas type II geometry is attractive based on the nature of “polar flattening” of the electron density around the Cl atom. The topological features derived at bond critical point (BCP) of Cl···Cl interactions also support the observed results.

Chapter 2 discusses hetero-halogen (Cl···F) and homo-halogen (F···F) intermolecular interactions involving “organic fluorine” in compounds 2-chloro-4-fluorobenzoic acid and 4-flurobenzamide respectively. Charge density distributions show polar flattening effects at both atoms Cl and F, however the extent of polarization is small on F in comparison with that of the Cl atom. 3D static deformation density plots depict δ*···δ− interactions for Cl···F intermolecular interactions while F···F interactions show small decreased repulsion features. The topological properties of F···F interactions bring out the similarity between F···F and Cl···Cl interactions.

Chapter 3 describes the nature of C–Cl···O=C halogen bond in 2, 5-dichloro-1, 4-benzoquinone, a molecule specifically chosen to depict this interaction dominantly. The topological values at bond critical point, three dimensional static deformation density features
and electrostatic potential isosurfaces unequivocally establish the attractive nature of C–Cl⋯O=C halogen bond in the crystalline lattice.

**Chapter 4** discusses the generation of multi-component systems (for example cocrystals and salts) of active pharmaceutical ingredients (API). Two systems associated with nicotinamide, one with salicylic acid and the other with oxalic acid as coformers resulting in 1:1 molecular complexes have been analyzed. The charge density analysis, particularly at the proton transfer region clearly bring out the differences between cocrystal and salt thus providing insights into the continuum in the proton transfer pathways in molecular crystals.

**Chapter 5** describes a new methodology [supramolecular synthon based fragment approach (SBFA)] concerning transferability of experimental charge density multipole parameters and building a database using well defined supramolecular synthons. The modularity and robustness of supramolecular synthons are used to transfer experimental charge density multipole parameters of synthons derived from a high resolution X-ray diffraction study to target molecules possessing these synthons as fragments in the crystalline lattice. The synthesized charge density and derived topological properties on target molecules using routine single crystal diffraction data are comparable with both experimental and theoretical charge density results. SBFA thus is expected to provide an additional database which can be applied to include intermolecular interactions space in the modeling directly unlike the available ones such as ELMAM, INVARIOM and UBDB. Further, SBFA approach can be extended to the determination and synthesis of charge density properties in macromolecules such as polypeptides, nucleic acids and proteins.

**APPENDIX** contains reprints of the articles published which comprises of the work carried out in addition to the above five chapters.