Chapter Eight

Conclusion and Future Prospects

The physicochemical properties of four important APIs and one bioactive molecule were improved by discovery and selection of solid-state forms such as polymorphs, amorphous form, cocrystals, salts etc.
This thesis covers the identification and characterization of new polymorphs of APIs (Chapter 2 and 3), and pharmaceutical cocrystals (Chapter 4, 5 & 6) and salts (Chapter 7) and the controlled modification of physicochemical properties such as solubility, dissolution rate and stability.

**Summary of Results**

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) and a COX-2 inhibitor. The native crystal structure of Nimesulide (or form I) has been characterized by X-ray powder diffraction lines whereas full 3D coordinates are known for a second polymorph (form II). A detailed structural characterization and phase stability of nimesulide polymorphs was carried out. Rod like crystals of Form I (space group $Pca2_1$, number of symmetry-independent molecules, $Z' = 2$, A and B) were crystallized from EtOH concomitantly with Form II ($C2/c$, $Z = 1$). These conformational polymorphs have different torsion angles at the phenoxy and sulfonamide groups. The crystal structures are stabilized by N–H···O hydrogen bonds and C–H···O, C–H···π interactions. The packing diagram for the two polymorphs shows a tape sequence of N–H···O2N hydrogen bond as XYYX in form I and XYXY in form II, viewed along the b-axis (Figure 1). Phase transition from the metastable form (II) to the stable modification (I) was studied using DSC, HSM, solid-state grinding, solvent-drop grinding, and slurry crystallization. The stable polymorph I was obtained in excess during solution crystallization, grinding and slurry methods. Intrinsic dissolution and equilibrium solubility experiments showed that the metastable form II dissolved much faster than the stable form I in pH 7 buffer (Figure 2). However stability of metastable form II is of concern since solid state grinding for 30 min in CH$_3$CN solvent assisted grinding gave the stable form I. The search for additives, coformers, excipients, and polymers to stabilize the metastable polymorph will be a practical way forward.
Curcumin, a hydrophobic phenol, is the principal curcuminoid in the popular Indian dietary spice turmeric. It is derived from the rhizome of the herb Curcuma longa. Curcumin is known for its diverse pharmacological activity such as an antioxidant, antimalarial, anti-carcinogenic, anti-HIV agent, etc. Curcumin is safe even at high dose of 12 g/day in animal and human experiments. Despite its efficacy and safety, curcumin is not approved as a therapeutic agent because of poor absorption and bioavailability, and rapid metabolism and systematic elimination. The crystal structure of stable form 1 ($P2/n$, $Z' = 1$) of curcumin is reported. During attempted cocrystallization experiments of curcumin, two new polymorphs, form 2 ($Pca2_1$, $Z' = 2$) and form 3 ($Pbca$, $Z' = 1$) were
obtained in the presence of 4-hydroxypyridine and pyrimidine respectively. A new amorphous phase was obtained from melt crystallization. Three crystalline polymorphs and one amorphous phase of curcumin are displayed in the Figure 3a. Form 2 amorphous dissolved 3.1 and 1.8 times faster than commercial form 1 in 40% EtOH-water medium (Figure 3b). The stabilization of form 2 and amorphous phase through additives, excipients, polymers, etc. could lead to the development of curcumin as a more bioavailable active ingredient.

**Figure 3** (a) Three crystalline polymorphs and one amorphous phase of Curcumin, (b) Dissolution rates of Curcumin polymorphs.
We report novel cocrystals of curcumin (1) with resorcinol and pyrogallol obtained by liquid-assisted grinding (Figure 4a). Curcumin–resorcinol (1a) (1:1) and curcumin–pyrogallol (1b) (1:1) cocrystals were characterized by X-ray diffraction, thermal analysis, FT-IR, FT-Raman, and ss-NMR spectroscopy. The 1:1 cocrystal stoichiometry is sustained by O–H···O hydrogen bonds between the phenolic OH groups of the coformers to the carbonyl group of curcumin. The melting point of the cocrystals is in between that of curcumin and the coformer and the lower melting cocrystal 1b is more soluble than higher melting 1a. The dissolution rates of curcumin-resorcinol (1a) and curcumin-pyrogallol (1b) in 40% EtOH–water are ~5 and ~12 times faster than that for curcumin (Figure 4b). The presence of water soluble phenolic coformers could be a reason for the improved aqueous solubility of curcumin. The present results on more soluble cocrystals of curcumin could provide faster dissolving solid forms of curcumin that are relatively stable for drug development. Pending in vivo clinical data, we believe that the faster dissolving curcumin cocrystals hint at improved bioavailability than pure curcumin.

The antitumor prodrug Temozolomide (TMZ) decomposes in pH ≥7 aqueous medium but is relatively stable in acidic conditions. Pure TMZ obtained as a white powder turns pink and then of brown color which is indicative of chemical degradation. Pharmaceutical cocrystals of TMZ were engineered with safe coformers (generally...
recognized as safe, GRAS chemicals) such as oxalic acid, succinic acid, salicylic acid, anthranilic acid, D,L-malic acid, D,L-tartaric acid, etc. to stabilize the drug as a cocrystal (Scheme 1). All cocrystals were characterized by FT-IR, FT-Raman, powder X-ray diffraction (PXRD), and single crystal X-ray diffraction. Temozolomide cocrystals with organic acids in the pKₐ range 2–6 were found to be more stable than the reference drug in physiological conditions. The half-life (T₁/₂) of TMZ–oxalic and TMZ–salicylic acid is two times longer than TMZ (3.5 and 3.6 h vs. 1.7 h), and TMZ–succinic acid, TMZ–tartaric acid and TMZ–malic also exhibited longer half life (2.3, 2.5, 2.8 h) in pH 7 buffer medium, indicating that cocrystals are more stable compared to the reference drug. The intrinsic dissolution rate (IDR) profile of TMZ–oxalic acid and TMZ–succinic acid cocrystals is comparable to that of TMZ whereas cocrystals with malic acid and salicylic acid dissolved faster than TMZ. Among the Temozolomide cocrystals examined, those with succinic acid, oxalic acid and salicylic acid exhibited improved stability and comparable or faster dissolution rate than the reference drug. Even TMZ–succinic acid cocrystals are stable in accelerated humidity conditions (40 °C and 75% RH) up to 28 weeks, whereas TMZ transformed to hydrate after 2 weeks and then converted to decomposed AIC hydrate after 5 weeks, confirmed from PXRD (Figure 5). Under accelerated ICH conditions of 40 °C and 75% RH, pure temozolomide turned pink to tan to dark brown in color due to degradation, TMZ–succinic acid and TMZ–oxalic acid cocrystal remained white (stable) for the entire duration. Along with stability, bioavailability or dissolution is equally important for a solid oral drug to be therapeutically effective. When the multiple criteria of physical form stability and dissolution rate and white color on storage are applied, TMZ–succinic acid and TMZ–oxalic acid appear to be the most promising pharmaceutical cocrystals for formulation development.
Scheme 1 Chemical structures of antitumor prodrug TMZ and GRAS coformers organic acid used as pH adjuster.

Figure 5 XRPD stack of TMZ and (b) TMZ−SA cocrystals kept at 40 °C and 75% RH, indicates that cocrystals is stable without degradation to TMZ or decomposed AIC even after 28 weeks, but TMZ transformed to monohydrate within 2 weeks and started to decompose within 5 weeks.

Niclosamide (NCL, Scheme 2) is an anthelmintic BCS class II drug having low solubility ($D_s=200$) and high permeability ($\log_{P_{ow}}=3.91$). To improve the solubility of niclosamide, pharmaceutical cocrystals were prepared with GRAS molecules e.g. caffeine (CAF), urea (URE), p-aminobenzoic acid (PABA), theophylline (THPH), nicotinamide (NCT) and isonicotinamide (INA) etc. Neat grinding, wet-granulation and slow evaporation methods were employed to synthesize niclosamide cocrystals. All the crystalline forms were characterized by m.p., FT-IR, X-ray diffraction to confirm purity of the bulk phases. Crystal structures of niclosamide and its cocrystals were
characterized by single crystal X-ray diffraction to know the structural aspects and hydrogen bonding in the molecular structure. The presence of intermolecular O–H···O hydrogen bond from hydroxyl to carbonyl group in niclosamide was replaced by acceptor atom of coformer in the cocrystalline phases. Cocrystals with nicotinamide and isonicotinamide were further characterized by $^{13}$C ss-NMR spectroscopy. All the cocrystals, except NCL–PABA, showed better powder dissolution rate than the reference API. Niclosamide–theophylline acetonitrile (NCL–THPHS) complex showed highest dissolution rate among all crystalline forms (Figure 6). But acetonitrile is a class II solvent, and has limits of toxicity. Comparatively NCL–THPH cocrystals showed moderate solubility and stability against hydration. Equilibrium solubility measurement showed that all the niclosamide cocrystals along with API converted to monohydrate within 24 h slurry experiment in 40% isopropanol-water medium. Search for new GRAS coformers with better improvement in solubility and stability of niclosamide is the next goal.

Scheme 2 Chemical structure of niclosamide (NCL) and coformers: caffeine (CAF), urea (URE), p-aminobenzoic acid (PABA), theophylline (THPH), nicotinamide (NCT) and isonicotinamide (INA). All niclosamide cocrystals maintain 1:1 stoichiometry.
Meclofenamic acid (MFA, Scheme 3) is the most potent anti-inflammatory drug among the fenamic acids. In this chapter are presented (1) two cocrystals of MFA with isonicotinamide (INA) and 4,4'-bipyridine (BPY); (2) polymorphs of MFA and piperazine (PPZ) 1:1 salt (orthorhombic $P\overline{2}_1\overline{2}_1\overline{2}_1$ and monoclinic $P2_1/c$), MFA–PPZ 1:1:1 salt hydrate, MFA–PPZ 2:1 salt; and (3) MFA and 2-aminopyridine (2-APY) 1:1 salt, MFA and 4-aminopyridine (4-APY) 1:1:1 salt hydrate. Sublimation of meclofenamic acid gave single crystals for X-ray diffraction which provided good quality data for refinement and all atomic coordinates. The cocrystal and salt structures are assembled via neutral $\text{O}^--\text{H} \cdots \text{O}, \text{O}^--\text{H} \cdots \text{N}, \text{N}^--\text{H} \cdots \text{O}, \text{N}^--\text{H} \cdots \text{N}$ and ionic $\text{O}^--\text{H} \cdots \text{O}^+, \text{N}^+--\text{H} \cdots \text{O}^-$ hydrogen bonds. The disorder of methyl group in meclofenamic acid crystal structure is absent in the cocrystal and salt structures, which contain different conformers (A or B) of methyl group orientation. The solubility of meclofenamic acid–isonicotinamide (1:1) and meclofenamic acid–4,4'-bipyridine (1:0.5) cocrystals is 2.9 and 7.6 times higher than that of MFA at 37 °C in 50% EtOH–water. Interestingly, MFA–PPZ 1:1 salt and its 1:1:1 hydrate are 2724 and 1334 fold more soluble than meclofenamic acid. Both these salts transformed in 50% EtOH–water slurry at 37 °C to 2:1 MFA–PPZ salt after 24 h, which
in turn transformed to meclofenamic acid after another 24 h of slurry stirring. Remarkably, the dissolution rate of MFA–PPZ (1:1) salt in water is just slightly lower than that of marketed sodium meclofenamate (Figure 7). This is the first example of polymorphic and variable stoichiometry piperazinium salts with X-ray crystal structures solved to good accuracy.

**Scheme 3** Piperazinium meclofenamate salts of variable stoichiometry obtained by liquid-assisted grinding.

![Scheme 3](image)

**Figure 7** Comparable dissolution rates of MFA–PPZ-M and MFA-SS in water
### Future Prospects

Stabilizing the metastable form and amorphous phase of API by addition of polymer, excipients etc. are an alternative to solubility manipulation. Salts are useful in terms of solubility improvement of APIs having ionizable functional groups. Pharmaceutical cocrystals are applicable for all APIs (both neutral/ionic) and provide dual advantage of solubility and stability improvement in same solid dosage form. Nutraceutical is a food or food product that reportedly provides health and medical benefits, including the prevention and treatment of chronic disease in addition to the basic nutritional value found in foods. Resveratrol (grapes), flavanoids e.g. catechin (green tea), quercetin (fruits), ellagic acid (strawberries), caffeine (coffee), theobromine (dark chocolates), anthocyanins (berries), citric acid (lemon), curcumin (turmeric), pyrogallol (amla) are well known Nutraceuticals (Figure 8). Nutraceuticals foods exhibit generally low solubility, and hence poor bioavailability and difficult to formulate as tablets or capsules. For e.g. curcumin (8.7 mg/L), resveratrol (30 mg/L), quercetin (2 mg/L) are poorly water soluble. Aqueous solubility of these Nutraceuticals could be enhanced by particle size reduction, hydrotropic agents, lyophilization, micelles, additives, and also new crystalline forms such as polymorphs, salts, or cocrystals.

![Chemical structures of few nutraceuticals having poor aqueous solubility.](image)

**Figure 8** Chemical structures of few nutraceuticals having poor aqueous solubility.
ABOUT THE AUTHOR

Pulash Sanphui, son of Late Mr. Indranath Sanphui and Mrs. Basanti Sanphui, was born in Bagaria, South 24 Paraganas district of West Bengal, India, in 1985. He completed his secondary school education at Srichanda M. N. M. Institution, Srichanda. He then completed his Intermediate education (2002) and B. Sc. (2005) from New Alipore College, Kolkata, affiliated to University of Calcutta. After the completion of his M.Sc. (Chemistry) from IIT Kharagpur (2005), West Bengal, he joined School of Chemistry, University of Hyderabad, to pursue PhD in 2007 under the supervision of Prof Ashwini Nangia. He qualified CSIR-UGC-National Eligibility Test for Junior Research Fellowship (JRF) held in December 2006 and June 2007 and was awarded research fellowship by the University Grant Commission (UGC) for 2007-2012 tenure (JRF and SRF). He has obtained 1st runner prize of K. V. Rao society memorial and Oration awards in the category of Young Research Scientist award in July 2011 for oral presentation on research work basis. He has attended and presented poster in XXII IUCR General Congress Assembly, held in Madrid, Spain on 22-30 August, 2011. He has presented lecture on research work basis in “Indo-US Bilateral meeting on Solid State Chemistry of drugs” held in Gurgaon, India on 2-4th February, 2012.
LIST OF PUBLICATIONS

1. Stable cocrystals of Temozolomide
   Ashwini Nangia, N. Jagadeesh Babu and Palash Sanphui,

2. Polymorphism in Isomeric Dihydroxybenzoic Acids

3. Polymorphism in Secondary Benzene Sulfonamides

4. Novel polymorphs and cocrystals of Curcumin
   Ashwini Nangia, Palash Sanphui, N. Rajesh Goud, U. B. Rao Khandavilli

5. Conformational polymorphs and phase transition in nimesulide

6. New polymorphs of Curcumin

7. Fast dissolving Curcumin cocrystals

8. Crystal Engineering of Stable Temozolomide Cocrystals

9. High Solubility Piperazine Salts of NSAID Meclofenamic Acid

10. Pharmaceutical cocrystals of Niclosamide
    Palash Sanphui, S. Sudalai Kumar and Ashwini Nangia*

_Palash Sanphui, Geetha Bolla and Ashwini Nangia*

(Manuscript under preparation).

**Symposium attended**

1. Indo–U.S. Workshop on Pharmaceutical Cocrystals and Polymorphs, Mysore, Feb 8-10, **2009**.


