10 Best papers highlighting the important discoveries/contributions

Papers are grouped in three categories highlighting the supersaturations in three drug delivery area

A. Value addition to the existing technology of amorphous solid dispersion and lipid formulations- Supersaturation maintenance and extended stability to the drug formulations

1. Ikjot Sodhi, **Abhay T Sangamwar**. Microarray plate method for estimation of precipitation kinetics of celecoxib under biorelevant conditions and precipitate characterisation. **Mol. Pharm.** (2018) 15(6):2423-2436

   Contribution: supersaturated state has been studied in a quantitative manner through microarray plate method with the application of classical nucleation theory (CNT) equation for determination of precipitation kinetics. The microarray plate method involves comprehensive measurements that allows for accounting of the nstochastic nature of nucleation and was directed to attain the principle of miniaturization. Overcoming the drawbacks of reproducibility and greater material requirement of existing methods, this study aims to quantify the phenomenon of *in vivo* precipitation along with capturing of precipitation profile through solid state characterization of model drug, celecoxib.

2. Ridhima Singh, Vaibhav Thorat, Harpreet Kaur, Ikjot Sodhi, Sanjaya K Samal, Kailash C Jena, **Abhay T Sangamwar**. Elucidating the molecular mechanism of drug-polymer interplay in a polymeric supersaturated system of rifaximin. **Mol. Pharm.** (2021) 18(4):1604–1621

   Contribution: The objective of this study is to inhibit the precipitation of rifaximin, involving screening of polymers at different concentrations, using in-house developed microarray plate method and solubility studies which set forth hydroxypropyl methylcellulose (HPMC) E15, Soluplus® and polyvinyl alcohol (PVA) to be effective precipitation inhibitors (PIs). Drug-polymer precipitates are examined for surface morphology by scanning electron microscopy, solid phase transformation by hot stage microscopy, and drug-polymer interaction by Fourier-transform infrared and nuclear magnetic resonance spectroscopy. Besides, the unfathomed molecular mechanism of drug-polymer interplay is discerned at the air-water interface using sum-frequency generation spectroscopy to correlate the interfacial hydrogen bonding properties in bulk water. Surprisingly, all studies disseminate HPMC E15 and Soluplus® as effective precipitation inhibitor of rifaximin.

3. Prachi Joshi, **Abhay T Sangamwar**. Insights into the role of compendial/biorelevant media on the supersaturation behavior of drug combination (drug-drug interaction) and precipitation inhibition by polymers. **AAPS PharmSciTech** (2022) 23(8):300

   Contribution: The objective of this study is to find precipitation of drug combinations in different compendial and biorelevant media (deionized water,

phosphate buffer pH 6.8, FaSSIF, and FeSSIF) and screening of the polymers for precipitation inhibition. Nine polymers were investigated at three different concentrations in terms of their drug-polymer solubility, *in vitro* precipitation behaviour, induction time, SHC, and droplet size. Although, all the polymers inhibit the precipitation of drugs, the extent of precipitation inhibition for Soluplus is high. The obtained drug-polymer precipitates were filtered, dried, and analyzed for amorphous/partial amorphous form using polarised light microscopy (PLM), differential scanning calorimetry (DSC), and powder X-ray diffractometry (PXRD). The drug-polymer interaction was examined using Fourier transform infrared (FTIR) spectroscopy and nuclear magnetic resonance (NMR) revealing the effect of polymers on drug precipitation.

4. Smiritilekha Mondal, Arvind Sirvi, Karan Jadhav, **Abhay T Sangamwar**. Supersaturating lipid based solid dispersion of atazanavir provides enhanced solubilization and supersaturation in the digestive aqueous phase **Int. J Pharm.** (2023) 638:122919

   Contribution: In this study we determined the extent of drug solubilization and supersaturation of supersaturating lipid based solid dispersion which is governed by formulation variables like drug payload, lipid composition, solid carrier properties and lipid to solid carrier ratio. Initially, the impact of lipid chain length and drug payload on drug solubilization in lipid preconcentrate and dispersibility were evaluated to design liquid lipid based formulation (LbF) of the model antiretroviral drug, atazanavir. The temperature induced supersaturation method enhanced the drug payload in medium chain triglyceride formulation at 60˚C. Further, the selected liquid supersaturated LbF was transformed into solid state LbF by employing different solid carriers including silica (Neusilin® US2 and Aerosil® 200), clay (Montmorillonite and Bentonite) and polymer (HPMC-AS and Kollidon® CL-M). The fabricated lipid based solid dispersions (LBSDs) were evaluated for solid state characterization to identify the physical nature of drug. *In vitro* digestion studies were conducted using pH-stat lipolysis method to assess the supersaturation propensity in aqueous digestive phase. Results revealed that LBSDs with silica and polymer carriers showed maximum drug solubilization throughout experiment compared to liquid LbF. The ionic interaction between drug-clay particles significantly reduced the atazanavir partitioning from clay based LBSDs. LBSDs with dual purpose solid carrier like HPMC-AS and Neusilin® US2 offers the potential to improve drug solubilization of atazanavir for physiologically relevant time. Lastly, we conclude that evaluation of formulation variables is crucial to achieve optimal performance of supersaturating LBSD.

5. Ajay Sanjay Lale, Arvind Sirvi, Shubha Debaje, Sadhana Patil, **Abhay T Sangamwar** Supersaturable diacyl phospholipid dispersion for improving oral bioavailability of brick dust molecule: A case study of aprepitant **Eur J Pharm Biopharm** (2024) 197:114241

   Contribution: This study aims to investigate the potential use of polymer inclusion in the phospholipid-based solid dispersion approach for augmenting the biopharmaceutical performance of Aprepitant (APT). Initially, different polymers

were screened using the microarray plate method to assess their ability to inhibit drug precipitation in the supersaturated solution and HPMCAS outperformed the others. Later, the binary (BD) and ternary (TD) phospholipid dispersions were prepared using the co-solvent evaporation method. Solid-state characterization was performed using scanning electron microscopy and powder X-ray diffraction to examine the physical properties, while molecular interactions were probed through FTIR and NMR analysis. *In vitro* dissolution studies were performed in both fasted and fed state biorelevant media. The results demonstrated a substantial increase in drug release from BD and TD, approximately 4.8 and 9.9 times higher compared to crystalline APT in FaSSIF. Notably, TD also showed a lowered dissolution difference between fed and fasted states in comparison to crystalline APT, indicating a reduction in the positive food effect of APT. Moreover, we assessed the impact of polymer inclusion on permeation under *in vitro* biomimetic conditions. In comparison with the crystalline APT suspension, both BD and TD demonstrated approximately 3.3 times and 14 times higher steady-state flux (Jss values), respectively. This can be ascribed to the supersaturation and presence of drug-rich submicron particles (nanodroplets) along with the multiple aggregates of drug with phospholipids and polymer in the donor compartment, consequently resulting in a more substantial driving force for passive diffusion. Lastly, *in vivo* pharmacokinetic evaluation demonstrated the enhanced absorption of both TD and BD over the free drug suspension in the fasted state. This enhancement was evident through a 2.1-fold and 1.3-fold increase in Cmax and a 2.3-fold and 1.4-fold increase in AUC0-t, respectively. Overall, these findings emphasize the potential of polymer-based phospholipid dispersion in enhancing the overall biopharmaceutical performance of APT.

6. Mehak Juneja, Krishna Mehtre, Vanshul Saini, Ridhima Singh, Prakash Amate, Mahesh Kashyap, **Abhay T Sangamwar**. Synergistic effect of polymers in stabilizing amorphous pretomanid through high drug loaded amorphous solid dispersion. **Drug Deliv. Transl. Res** (2024)

Contribution: The present investigation aimed to develop high drug loaded ternary amorphous solid dispersions (ASDs) of pretomanid (PTM) with improved stability and enhanced biopharmaceutical performance by utilizing a combination of polymers. The polymers were comprehensively screened based on drug-polymer miscibility and saturation solubility analysis. A combination of Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS-HF) and Polyvinylpyrrolidone K-30 (PVP K-30) showed synergism in drug-polymer miscibility as evidenced through pronounced depression in the melting endotherm of PTM. The Powder X-ray Diffraction (P-XRD) diffractograms of 30% *w/w* PTM loaded ternary ASDs displayed the halo pattern, contrary to the binary ASDs. Drug-polymer interactions (hydrophobic forces) involved between PTM and polymers were detected through Fourier Transform Infrared Spectroscopy (FT-IR) and Nuclear Magnetic Resonance Spectroscopy (13C-NMR) which contributed to the synergistic enhancement in solubility and dissolution of ternary ASDs with sustained release over 12 h. Ternary ASDs demonstrated better in-vivo performance compared to the binary ASDs, showing a 4.63-fold increase in maximum plasma concentration. All ASDs remained stable and resisted phase separation during short-term stability studies for 3 months at ambient conditions.

It was concluded that the hydrophobic and hydrophilic polymeric combination (HPMCAS-HF and PVP K-30, respectively) effectively prevented the crystallization and ensured sustained drug release with improved in-vivo absorption of PTM.

B. Amorphous salt solid dispersion-An extension to the existing technology

7. Sumit Mukesh, Prachi Joshi, Arvind Bansal, Mahesh Kashyap, Sanjay Mandal, Vasant Sathe, **Abhay T Sangamwar**. Amorphous salt solid dispersions of celecoxib: Enhanced biopharmaceutical performance and physical stability. **Mol. Pharm.** (2021) 18(6):2334-2348

   Contribution: The present investigation elaborates a combined strategy of amorphization and salt formation for celecoxib (CEL), providing the benefits of enhanced solubility, dissolution rate, in vivo pharmacokinetics, and physical stability. We generated amorphous salts solid dispersion (ASSD) formulations of CEL via an in situ acid− base reaction involving counterions (Na+ and K+) and a polymer (Soluplus) using the spray-drying technique. The generated CEL-Na and CEL-K salts were homogeneously and molecularly dispersed in the matrix of Soluplus polymer. The characterization of generated ASSDs by differential scanning calorimetry revealed a much higher glass-transition temperature (Tg) than the pure amorphous CEL, confirming the salt formation of CEL in solid dispersions. The micro-Raman and proton nuclear magnetic resonance spectroscopy further confirmed the formation of salt at the –S=O position in the CEL molecules. CEL-Na-Soluplus ASSD exhibited a synergistic enhancement in the aqueous solubility (332.82-fold) and in vivo pharmacokinetics (9.83-fold enhancement in the blood plasma concentration) than the crystalline CEL. Furthermore, ASSD formulations were physically stable for nearly 1 year (352 days) in long-term stability studies at ambient conditions. Hence, we concluded that the ASSD is a promising strategy for CEL in improving the physicochemical properties and biopharmaceutical performance.

8. Sumit Mukesh, Goutam Mukherjee, Ridhima Singh, Nathan Steenbuck, Carolina Demidova, Prachi Joshi, **Abhay T Sangamwar**, Rebecca C Wade. Comparative analysis of drug-salt-polymer interactions by experiment and molecular simulation improves biopharmaceutical performance. **Comm Chem** (2023) 6:201

   Contribution: Here, we describe a comparative experimental and computational characterization of amorphous solid dispersions containing the drug celecoxib, and a polymer, polyvinylpyrrolidone vinyl acetate (PVP-VA) or hydroxypropyl methylcellulose acetate succinate, with or without Na+/K+ salts. Classical models for drug-polymer interactions fail to identify the best drug-salt-polymer combination. In contrast, more stable drug-polymer interaction energies computed from molecular dynamics simulations correlate with prolonged stability of supersaturated amorphous drug-salt-polymer systems, along with better dissolution and pharmacokinetic profiles. The celecoxib-salt-PVP-VA formulations exhibit excellent biopharmaceutical performance, offering the prospect of a low-dosage regimen for this widely used anti-inflammatory, thereby increasing cost-effectiveness, and reducing side-effects.

C. Lipophilic salts and lipid based formulations

9. Karan Jadhav, Arvind Sirvi, Akash Janjal, Mahesh C Kashyap, **Abhay T Sangamwar**. Utilization of lipophilic salt and phospholipid complex in lipid based formulations to modulate drug loading and oral bioavailability of pazopanib. **AAPS PharmScitech** (2024) 25(59)

   Contribution: Pazopanib hydrochloride (PAZ) displays strong intermolecular interaction in its crystal lattice structure, limiting its solubility and dissolution. The development of lipid-based formulations (LbFs) resulted in reduced PAZ loading due to solid-state mediated low liposolubility. This study aims to enhance our understanding of PAZ crystallinity by synthesizing a lipophilic salt and phospholipid complex and investigating its impact on the drug loading in LbFs. The synthesized pazopanib lipophilic salt and phospholipid complex were extensively characterized. The solid form of pazopanib docusate (PAZDOC) and pazopanib phospholipid complex (PAZ-PLC) indicates a reduction in characteristic diffraction peaks of crystalline PAZ. The lipid formulations were prepared using synthesized PAZ-DOC and PAZ-PLC, where PAZ-DOC demonstrated six-fold higher drug solubility than the commercial salt form and twice that of the PAZ-PLC due to differences in the crystallinity. Further, the impact of salt and complex formation was assessed on the aqueous drug solubilization using lipolysis and multimedia dissolution experiments. Moreover, the LbFs showed notably faster dissolution compared to the crystalline PAZ and marketed tablet. In terms of in vivo pharmacokinetics, the PAZDOC LbF exhibited a remarkable 11-fold increase in AUC value compared to the crystalline PAZ and a 2.5-fold increase compared to VotrientTM. Similarly, PAZ-PLC LbF showed an approximately 9-fold increase in drug exposure compared to the crystalline PAZ, and a 2.2-fold increase compared to VotrientTM. These findings suggest that disrupting the crystallinity of drugs and incorporating them into LbF could be advantageous for enhancing drug loading and overcoming limitations related to drug absorption.

10. Arvind Sirvi, Karan Jadhav, **Abhay T Sangamwar**. Enabling superior drug loading in lipid based formulations with lipophilic salts for a brick dust molecule: Exploration of lipophilic counterions and in vitro-in vivo evaluation **Int. J Pharm**. (2024) 6556, 124108.

    Contribution: The study aimed to enhance drug loading in lipid preconcentrate for Nilotinib (Nil) through complexation or salt formation with different lipophilic counterions. We synthesized different lipophilic salts/ complexation via metathesis reactions and confirmed by ^{1}H-NMR and FTIR. Aliphatic sulfate-based lipophilic salt showed improved solubility in MCT (~27-30 fold) and LCT (~13-15 fold) based lipids compared to crystalline Nil. The increased lipid solubility could be attributed to the reduction in drug crystallinity which was further confirmed by the PXRD and DSC. Prototype lipid based formulations (LbFs) were prepared to evaluate drug loading and their physicochemical characteristics. The findings suggested that chain length and polarity of counterions affect the drug loading in LbF. In addition, physical stability testing of formulations was performed, inferring that aliphatic sulfate-based LbFs were stable with no sign of drug precipitation or salt disproportionation. An in vitro lipolysis-permeation study revealed that the primary driver of absorptive flux is the solubilization of the drug and reduced amount of lipid. Further, the in vivo

characterization was conducted to measure the influence of increased drug load on oral bioavailability. Overall, the results revealed enhanced absorption of lipophilic salt based LbF over crystalline Nil and conventional LbF which supports the idea that lipophilic salt-based LbF enhances drug loading, and supersaturation-mediated drug solubilization, unlocking the full potential of LbF.