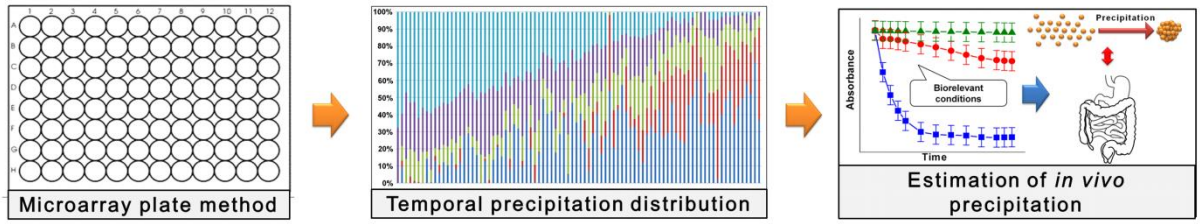
Details of the research work duly signed by the applicant for which the Sun Pharma Science Foundation Research Fellowship is claimed

Focus of the Prof Abhay's laboratory at NIPER SAS Nagar is 'Development of oral drug delivery systems that survive gastrointestinal transit and pass over the intestinal barrier'. Most drugs are taken orally, as tablets or capsules, for example. However, designing these pharmaceutical products is such a way that the active ingredient is absorbed at an appropriate rate and extent by the gut is far from easy. Abhay's laboratory projects are set out to enhance our understanding of how orally administered drugs are taken up from the gastrointestinal (GI) tract into the body and apply this knowledge to create new delivery system and test and tools that will better predict the performance of these drugs in patients. Abhay's laboratory has four goals: 1) Improved drug loading in oral formulations 2) Reduced premature release of drugs in gastrointestinal tract (GIT) 3) Enhanced equilibrium solubility of drugs and 4) Reduced amount of drug in the formulation to reach the therapeutic dose. He applies the prominent strategy to address the key gaps in our knowledge of GI drug absorption and deliver a framework for oral drug delivery. The strategy include a novel prospective investigation to define drug specific methodologies, extensive validation of novel and existing biopharmaceutics tools using drugs and a combination of in vitro and in silico characterization of drugs and formulations integrated into physiologically based in silico biopharmaceutics models capturing the full complexity of GI drug absorption.

Prof Abhay claims the Sun Pharma Science Foundation Research Fellowship on his work '**Design and development of supersaturated oral drug delivery systems (SDDS) by modulating intraluminal drug and formulation behaviour of difficult-to-formulate drugs**'. Supersaturated drug delivery system hold the promise of enabling intestinal absorption for difficult-to-formulate poorly soluble drug candidates based on a design approach that included 1) converting the drug into a high energy or rapidly dissolving system which presents a supersaturated solution to the GI environment and 2) dosage form components that act to stabilize the formed metastable drug solution through nucleation and/or crystal growth inhibition. Supersaturation is a thermodynamically metastable state that constitutes the driving force for precipitation. Therefore the clinical benefit of SDDS in enhancing drug bioavailability will greatly depend on the stability of the induced supersatuarated state and, hence the kinetics of precipitation. Appropriate evaluation of supersaturation, precipitation and possibly precipitation inhibition is therefore key for the efficient development and optimization of SDDS, as the in vitro evaluation of intraluminal

SDDS behaviour is burdened with practical difficulties, efforts have been directed to the development of predictive in vitro precipitation assays. A general supersaturation assay involves generation of supersaturation through either solvent shift or pH changes followed by capturing of precipitation process through either direct monitoring precipitated particles by turbidimetry, nephelometry, focused beam reflectance measurement (FBRM) or dynamic light scattering or indirectly through measurement of the decline of solute concentration in media through UV spectrophotometry or HPLC analysis.

Prof Abhay initiated the work on microarray plate in 2017 with his PhD student Ms Ikjot Sodhi. Microarray plates have potential of overcoming disadvantages of bulky supersaturation assays and decrease analysis time by increasing replicates and lowering sample size. This tool has already found its niche in the domain of crystallization as a screening tool with applications varying from selecting conditions suitable for crystallization of macromolecules[1] to screening of excipients as precipitation inhibitors for amorphous solid dispersion.[2] Dai *et al.*, demonstrated the use of a 96-well plate to assess the precipitation kinetics of three liquid formulations of a new molecular entity (NME) with different precipitation kinetics in biorelevant media through analysis by high performance liquid chromatography (HPLC).[3] Microplate assays combining quantitative analysis of supernatant with turbidimetry have also been demonstrated as a screening tool to rank-order supersaturation limits of early drug candidates.[4] Microplate based assays are hence gaining recognition in the domain of assessment of supersaturation stabilization and precipitation kinetics. Prof Abhay has published a paper on the study aimed at understanding the precipitation behavior of a model drug, celecoxib (CEL), under biorelevant conditions. The precipitation kinetics was assessed through a microarray plate method involving a comprehensive number of measurements and application of CNT for assessment of nucleation rates. Further, precipitation kinetics was also studied in certain components of biorelevant media in order to identify the factors unfavorable for supersaturation of CEL. The study also introduces two-dimensional plots termed “temporal precipitation distribution” diagrams that represent the degree of precipitation in different time intervals. Solid state characterization and optical microscopy were performed to assess the nature of drug reprecipitated under biorelevant conditions.[5]



A review article on stabilizing supersaturated drug delivery system through mechanism of nucleation and crystal growth inhibition of drugs is authored by Prof Abhay and his PhD student Ms Prachi Joshi and published at Therapeutic Delivery. [6] This article cover maintenance of supersaturated solution in the GI tract, the prime requirement for enhanced oral absorption of poorly soluble drugs; stabilization is required because of their unstable nature. Various mechanisms namely hydrogen bond formation, molecular weight and hydrophobic interactions, steric hindrance, increasing viscosity of solution and stabilization of metastable polymorphs through which a supersaturated system can be stabilized, the main mechanism of precipitation inhibition is through hydrogen bond formation whereas the other mechanisms vary with drug and polymer properties. These interactions can be identified using various spectroscopic methodsnamely IR, NMR, Raman and molecular modeling, which are used to investigate the drug–polymer interactions. The supersaturated systems are applicable to various dosage forms for enhanced oral drug delivery. There are various marketed formulations that generate supersaturated solution on dissolution, and hence enhance the oral bioavailability.

Assessment of biopharmaceutical performance of supersaturated drug delivery system is non-predictive as these formulations are prone to phase transformation to stable crystalline form due to high energy physical form. Prof Abhay in collaboration with inter-niper research group of Prof Bansal predicted the biopharmaceutical performance of SDDS using in vitro kinetic solubility and dissolution rate constant in the biorelevent medium with a case study of carbamazepine.[7]

After the successful completion of microarray plate method which allows comprehensive replicates and decent statistics that make the method an edge over the other exploratory assays, Prof Abhay moved forward for precipitation inhibition efficacy of polymers for SDDS in difficult-to-formulate drugs. In vitro supersaturation assessment of drugs generally involve monitoring of molecularly dispersed drug as a function of time after its addition in a test medium at levels exceeding the equilibrium solubility. There are other developed methods of supersaturation generation that include solvent evaporation or freezing, addition of ions that participate in the precipitation process, dissolution of unstable high energy forms,

change of temperature that find applicability in the fields of biotechnology and batch crystallization.[8]. Solvent shift method and pH shift method are employed for assessment of non-formulated drugs. Solvent shift method involves introduction of concentrated solution of drug in a good solvent into the test media. The solubility difference between the good solvent and media leads to generation of supersaturation. pH shift method is utilized for ionizable drugs where change in pH generates supersaturation of its neutral state. Another pH shift based method involves chasing equilibrium solubility as embodied in the CheqSol® system of Sirius.[9] High throughput supersaturation assays have been pursued through 96-well based high throughput formats that evaluate the capacity of excipients on supersaturation.[10-11] While this tool has been adapted to simply rank-order supersaturation limits of drug candidates for use as a screening tool, methods have also been developed to quantitatively assess the precipitation kinetics of drugs under biorelevant conditions. Prof Abhay attempts to assess the effect of polymers on precipitation behaviour of a model drug in order to evaluate their supersaturation stabilizing potential. Spectrophotometry-based microarray plate method was adopted for the purpose. Quantitative assessments were made through application of Poisson distribution and measurement of area under curve (AUC) of the precipitation process. Particle-level insights of events observed during precipitation were analysed through focused beam reflectance measurements (FBRM). Powder X-ray diffraction (PXRD) analysis revealed the solid state character of the formed precipitates while scanning electron microscope (SEM) imaging showed the impact of polymers on topography and surface character of formed precipitates. [12]

Supersaturating drug delivery systems (SDDS) are able to generate higher concentration of drugs in the gastrointestinal lumen much beyond their thermodynamic solubility. However, supersaturated state is metastable in nature and has the tendency to precipitate. This precipitation can be eventually prevented by using precipitation inhibiting excipients like polymers which, even in low concentrations, maintain supersaturated state for suitable time of drug absorption. Understanding the mechanisms of polymer mediated precipitation inhibition would enable a formulation scientist to design stable formulations. Prof Abhay move forward for molecular level understanding of drug-polymer interactions that play a role in stabilizing the supersaturated state of a BCS class II drug, atorvastatin calcium (ATC). Polymers were screened on the basis of quantitative supersaturation assays which showed differential activity on nucleation and crystal growth of ATC, estimated through impact on induction and crystal growth time, respectively. The precipitates obtained from supersaturation assays were subjected to Fourier Transform-Infrared spectroscopy (FTIR)

analysis and 1H Nuclear Magnetic Resonance (NMR) to get insights on drug-polymer interactions leading to supersaturation stabilization. ATC showed stronger interaction with EUD EPO as compared to PVP K30 in proton NMR studies. For nucleation to occur, ATC molecules should overcome these drug-polymer interactions to diffuse and form critical nucleus. The polymer assisted supersaturation of ATC has shown 20-fold increase in the permeability, assessed through Caco-2 study, when compared to saturated solution of ATC. In conclusion, polymer-stabilized ATC supersaturation is successful in maintaining the solubility advantage of ATC along with delivering the transmembrane permeability enhancement. [13]

Furthermore, Prof Abhay studied a drug Rifaximin (RFX) which is a nonabsorbable BCS class IV drug approved for the treatment of irritable bowel syndrome and effective against Helicobacter pylori. RFX shows slow crystallization and precipitation in an acidic pH of 1.2−2, leading to obliteration of its activity in the gastrointestinal tract. The objective of the study was to inhibit the precipitation of RFX, involving screening of polymers at different concentrations, using an in-house developed microarray plate method and solubility studies which set forth hydroxypropyl methylcellulose (HPMC) E15, Soluplus, and polyvinyl alcohol to be effective precipitation inhibitors (PIs). Drug− polymer precipitates (PPTS) were examined for surface morphology by scanning electron microscopy, solid-phase transformation by hot stage microscopy, the nature of PPTS by polarized light microscopy, and drug−polymer interactions by Fourier transform infrared and nuclear magnetic resonance spectroscopy. Besides, the unfathomed molecular mechanism of drug−polymer interplay was 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 PIs of RFX. [14]

Combination drug therapy (CDT) plays an immense role in the treatment of various diseases such as malaria, hypertension, cancer, HIV-AIDS, helminthiasis, and many more. However, *in vitro* drug-drug interaction (DDI) is not well reported for better efficacy of CDT. In DDI one drug may enhance the precipitation of other drugs thereby reducing the advantage of CDT.Prof Abhay reported DDI in terms of *in vitro* precipitation of drugs with albendazole and mebendazole. This may be the first report to propensate the possibility of either drug precipitation in the combination. These drugs are categorized into BCS class II weak base and hence have tendency to precipitate in the gastrointestinal tract. The objective of this study was 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 behavior, induction time, supersaturation holding capacity and droplet size. Although, all the polymers inhibit the precipitation of drugs, the extent of precipitation inhibition for Soluplus was 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. These insights may further be used in the formulation of CDT for helminthiasis management. [15]

Understanding and controlling the drug solubilization in digestive environment is of great importance in the design of lipid based solid dispersion (LBSD) for oral delivery of poorly aqueous soluble drugs. Prof Abhay and his group have 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 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 ATZ 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 ATZ for physiologically relevant time. Lastly, we conclude that evaluation of formulation variables is crucial to achieve optimal performance of supersaturating LBSD. [16].

In another approach Prof Abhay investigated 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 SEM and PXRD 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, the group 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 AUC_{0}-t, respectively. Overall, these findings emphasize the potential of polymer-based phospholipid dispersion in enhancing the overall biopharmaceutical performance of APT. [17]

Lipid-based formulations (LbFs) have demonstrated success in pharmaceutical applications; however, challenges persist in dissolving entire dose of a drug into defined liquid volumes. Prof Abhay and his group proceed for a novel study of te temperature-induced supersaturation method was employed in LbF to address drug loading and pill burden issues. Supersaturated LbFs (super-LbF) were prepared using the temperature-induced supersaturation method, where the drug load is above its equilibrium solubility. Further, the influence of drug's physicochemical and thermal characteristics on drug loading and their

relevance with an apparent degree of supersaturation (aDS) was studied using two model drugs i.e. ibrutinib and enzalutamide. All the prepared LbFs were evaluated in terms of physical stability, dispersion, and solubilization capacity, as well as pharmacokinetic assessments. Observations revealed drug recrystallization within the lipid solution after 60 days of storage. It was noted that the physical stability of Super-LbF was dependent on the inherent characteristics of the drug and the achieved aDS in the lipid solution. The dispersion results showed that the aDS had a significant effect on the dispersion behavior of LbFs. Furthermore, high-throughput lipolysis studies demonstrated a significant decrease in drug concentration across all LbFs (regardless of drug loading) due to decline in the formulation solvation capacity and subsequent generation of *in-situ* supersaturation. Overall, short duration of the thermodynamic metastable state limits the potential absorption benefits. Further, the *in vivo* results demonstrated comparable pharmacokinetic parameters between conventional LbF and super-LbF, with both formulations exhibiting superior profiles compared to the crystalline drug suspension. In summary, this study emphasizes the potential of temperature-induced supersaturation in LbF for enhancing drug loading and highlights the intricate interplay between drug properties, formulation characteristics, and *in vivo* performance.[18]

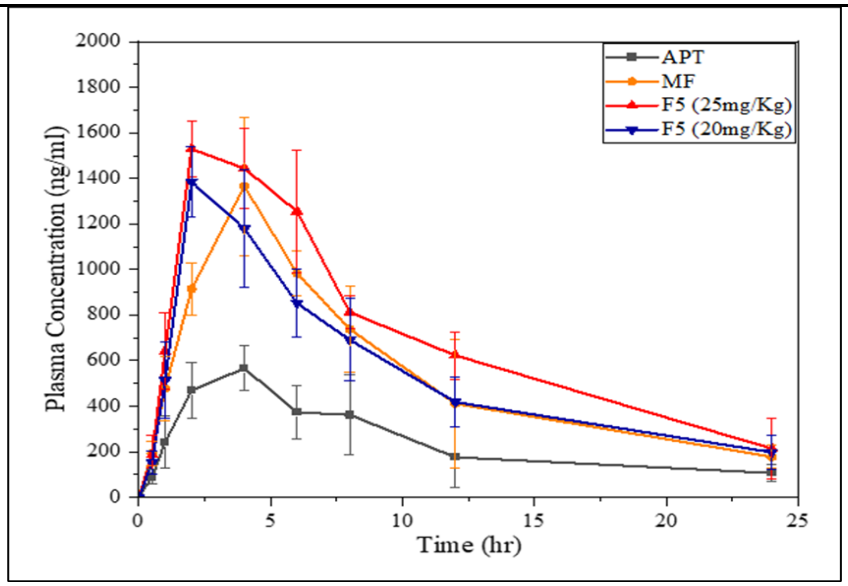
Recently, Prof Abhay and his group completed a novel work on **Ternary cellulosic dispersion formulations of aprepitant for pharmaceutical bio-performance enhancement from integrated in silico and experimental workflow.** Aprepitant (APT), the selective neurokinin I receptor antagonist is an antiemetic BCS class IV drug with Log P 4.5 and pKa of 2.4 (weak base) and 9.7 (weak acid), associated with dissolution rate limited per oral absorption and uncontrolled *in vivo* precipitation in the intestinal lumen with increased dose leading to its compromised bioavailability. [19]. Moreover, the moderate glass transition temperature (T_g) of 91^0C could lead to poor physical stability at high temperature. The prevalent use of APT in immunocompromised patients would lead to global market value of 537.7 million USD by 2029 and compound annual growth rate (CAGR) of 4.3% during the forecast period (2023-2029) [*Global Market Growth 2023-2029. Market Research Reports*, GIR052307352 (2023)]. The administration of marketed formulation EMEND® is recommended with food attributable to the positive food effect of APT in order to increase its absorption but because of the diversity in the food intake habit, led to erratic drug absorption at higher doses and interpatient variability in the pharmacokinetic parameters. Further, the treatment requires heavy dosage regimen with a loading dose of 125 mg once a day (OD) on

day 1 followed by the maintenance dose of 80 mg OD on day 2 & 3 during long-term chemotherapy treatment in cancer, acquired immune deficiency syndrome (AIDS) etc., which increase the side effects and cost of therapy leading to poor patient compliance. [20]. Thus, there is need of an hour to develop a formulation of APT which ameliorates its biopharmaceutical properties and reduces the dose, which would be more economical and beneficial for the mankind. Several attempts are made to develop various drug delivery systems in order to address the existing problems of APT viz., chitosan nanosuspension [21], super-self-nanoemulsifying drug delivery systems [22], phospholipid-based solid dispersions , ternary amorphous solid dispersions (TASD) including surfactant-polymer combination [23], liquisolid formulation, crystalline nanosuspension , amorphous nanoparticles, microemulsion, cyclodextrin inclusion complex. Among the aforementioned technologies, ASD is one of the promising, simplistic and cost-effective approaches to augment the biopharmaceutical performance of APT. In ASDs polymer plays a significant role in maintaining supersaturated concentration of drug thereby increasing its solubility/dissolution . However, the amorphous form of drug in the ASDs is metastable and tends to recrystallize either during dissolution or long-term storage resulting in the loss of attained benefits. To conquer the issue, ternary amorphous solid dispersions (TASDs) took over the binary ASDs which involve the incorporation of third component into drug-polymer system. Most of the TASDs reported comprise of dispersion of drug in polymer-surfactant matrix. The surfactants are generally added to enhance the wettability, drug-polymer miscibility, dissolution, supersaturation and, bioavailability of drug [24]. Nevertheless, it was found that some of the surfactants at critical hemi-micelle concentration assist the recrystallization process of drug from the supersaturated solution and hamper the permeation across GI membrane. Thus, the selection of third component in TASD is the critical step as it could hamper the performance of formulation. To alleviate the negative impact of surfactant, polymers come into play and added as a third component in the drug polymer system. The combination of polymers proved to be advantageous in improving the physical stability, inhibiting precipitation and sustaining the release, thereby increasing bioavailability. The molecular level drug-polymer interactions play a major role in choosing the appropriate polymer for a drug which further decides the drug-polymer miscibility, equilibrium solubility and extent of supersaturation [25]. The polymers in combination are chosen on the basis of their hydrophilic/hydrophobic characteristics for getting the synergistic effect of enhanced solubility and supersaturation maintenance. The study aimed to optimize the bio-performance of low-dosed APT by utilizing the amalgamation of cellulosic polymers for the development of advanced

supersaturated ternary amorphous solid dispersions of APT by spray drying method for maintaining supersaturation and augmenting biopharmaceutical performance of APT. The study progresses systematically, encompassing PSA through GastroPlus® to identify the factors limiting the absorption of APT, polymer screening through supersaturation assay, selection of hydrophilic and hydrophobic polymer in combination through drug-polymers interaction studies, formation of drug-polymer precipitates and supersaturated amorphous systems at different drug loadings followed by *in vitro in vivo* evaluation. In response to the evolving landscape of pharmaceutical research, we highlighted the emergence of computational *in silico* modeling as a powerful tool for polymer screening. This contemporary approach gives more valuable insights than conventional mathematical approach viz., determination of drug-polymer miscibility parameters, and assists in the better selection of suitable polymers [26]. Moreover, the molecular-level drug-polymer interactions were revealed and correlated by high-end analytical techniques viz., nuclear magnetic resonance (NMR) and Fourier transform infrared (FTIR) spectroscopy and *in silico* MD simulation studies which play a significant role in modulating the bioavailability of APT and APT-APT aggregation. Further, the formulations were investigated for, improvement in dissolution/solubility, precipitation inhibition, and prolonged physical stability. The amorphous nature of formulations was proved by X-ray powder diffraction (XRPD) and polarized light microscopy (PLM) and the morphological alterations were analyzed by scanning electron microscopy (SEM). *In vivo* pharmacokinetic (PK) studies in rats were also performed at both equivalent and reduced dose of marketed formulation, to unveil the real-world implications and, prediction of PK parameters using developed physiological based absorption model (PBAM) in GastroPlus® and *in vitro in vivo* correlation *(IVIVC)* was done. The outcomes obtained in the studies suggested, the better *in silico-in vitro-in vivo* correlation would assist in the development of successful formulation of APT, which would be the promising approach in alleviating the existing biopharmaceutical problems. Furthermore, the cost-effectiveness of the technology and lower dose of APT could improve the pharmaceutical economics and hold the promise of promoting patient compliance through a more manageable dosage regimen. In the figure low dose formulation F5 present equal Cmax in comparison to the marketed formulation (MF).

Parameter	**T_{max} (**h)	**C_{max}** (ng/mL)	**$AUC_{(0-t)}$** (ng/mL)*h
APT	4	611.98 ± 71.06	5940.14 ± 912.89

MF	4	1407.76 ± 223.03	13094.24 ± 2150.33
F5 (25 mg/kg)	2	1599.26 ± 69.41	16967.3 ± 772.19
F5 (20 mg/kg)	2	1452.06 ± 115.79	13208.11 ± 1090.04

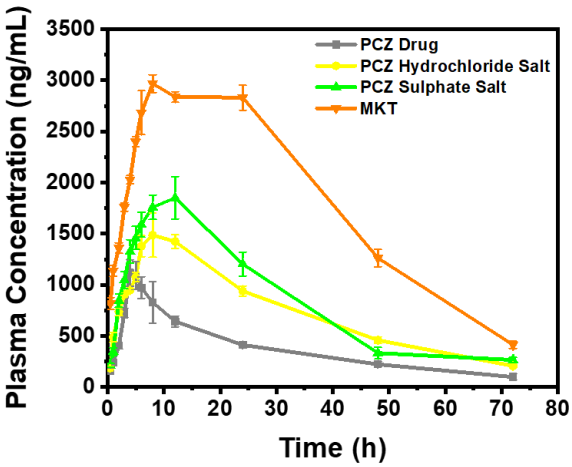


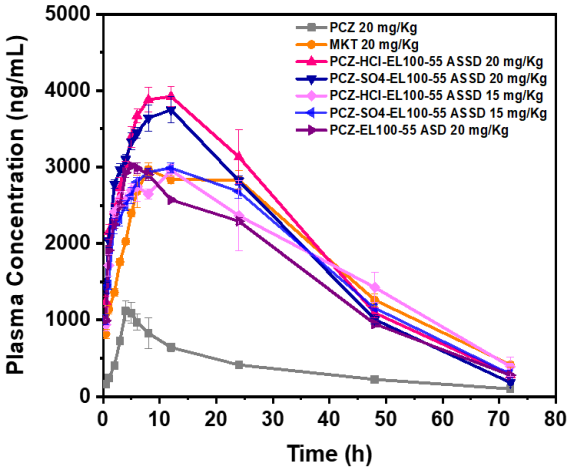
Prof Abhay and his team has worked on another molecule, posaconazole. He presented a novel work of amorphous salt solid dispersion (ASSD) after preparation of posaconazole salts. The data presented here show higher plasma concentration of salts that posaconazole. The ASSD preparations in the lower concentration shoe similar plasma concentration to the marketed formulation. This approach is best suitable for low dose preparaions of the posaconazole.

In vivo Pharmacokinetic Studies

The pharmacokinetic performance of the drug posaconazole (PCZ) and its salt formulations was done to assess the *in vivo* bioavailability of PCZ in its salts form and amorphous form. The study was executed in Wistar rats which were administered PCZ and its salts formulations per oral followed by the collection of blood samples at fixed time points. The plasma was separated and further processed to analyse through developed bioanalytical HPLC method. The outcomes revealed, crystalline PCZ showed a maximum plasma concentration (C_{max}) of 1253.855 ng mL^{-1} at t_{max} of 5.2 h whereas its hydrochloride and sulphate salts showed C_{max} of 1607.212 ng mL^{-1} (at 8.4 h) and 1926.735 ng mL^{-1} (at 10.4 h), respectively. The PCZ salts showed 1.615 and 2-folds increase in t_{max} and, 1.966- and 2.261-folds increase in the AUC of PCZ hydrochloride and sulphate salts, respectively wrt to PCZ free base which revealed the prolonged maintenance of higher concentration of PCZ. The

PCZ amorphous salt solid dispersions (ASSD) outperformed the drug, amorphous solid dispersions (ASD) and marketed formulation. The PCZ-HCl-EL100-55 ASSD showed 3.179-, 1.318- and 1.309-folds increase in C_{max} wrt to drug, marketed formulation and ASD, respectively. Moreover, the prolonged T_{max} of ASSD up to 13.6 h wrt to lower T_{max} of aprox. 5 h in case of drug and ASD at same dose (20 mg/Kg), showcased ASSD formulations were able to maintain the higher concentration of PCZ in plasma above minimum inhibitory concentration (MIC) for prolonged time, suggesting improved antifungal effect. The AUC of 148032.200 ng.h/ml was obtained for PCZ-HCl-EL100-55 ASSD which was 5.550-folds more than drug's AUC (26671.451 ng.h/ml), 1.135-folds wrt marketed formulation and 1.304-folds wrt ASD. The outcomes suggested that the synergistic effect of both salt formation and amorphization of crystalline form of drug plays an important role in addressing the existing challenges of poorly water-soluble drugs by enhancing the solubility and supersaturation maintenance of drug in its amorphous form. The PCZ in ionic state in its salt form and in ASSD revealed better intermolecular interactions between drug, counterion and polymer in comparison to weaker interactions between drug and polymer in case of ASD suggesting the prolonged supersaturation maintenance in salt formulations of PCZ indicated by their enhanced T_{max}. The results were considered statistically significant with p value < 0.05. Moreover, the ASSD even at lower dose (15 mg/Kg) showed similar pharmacokinetic profile wrt marketed and ASD formulations at 20 mg/Kg dose indicating bioequivalence among the formulations and the p value was found to be non-significant in statistical analysis. This further suggested the reduction in heavy dosage regimen of PCZ offering the prospect of a low-dosage regimen for this high priced widely used antifungal agent, thereby increasing cost-effectiveness, improved patient compliance and reducing side-effects.





References:

1. Chait, A.; DeLucas, L.; Stoops, B.; Belgovskiy, A. Method forpreparation of microarrays for screening of crystal growth conditions. U.S. Patent 7,244,396, July 17, 2007
2. Hu, Q.; Wyttenbach, N.; Shiraki, K.; Choi, D. S. Miniaturized Screening Tools for Polymer and Process Evaluation. In Amorphous Solid Dispersions: Theory and Practice; Shah, N., Sandhu, H., Choi, D. S., Chokshi, H., Malick, A. W., Eds.; Springer: New York, 2014; pp 165−195.
3. Dai, W. G.; Dong, L. C.; Shi, X.; Nguyen, J.; Evans, J.; Xu, Y.; Creasey, A. A. Evaluation of drug precipitation of solubility enhancing liquid formulations using milligram quantities of a new molecular entity (NME). J. Pharm. Sci. 2007, 96 (11), 2957−2969.
4. Morrison, J. S.; Nophsker, M. J.; Haskell, R. J. A Combination Turbidity and Supernatant Microplate Assay to Rank Order the Supersaturation Limits of Early Drug Candidates. J. Pharm. Sci. 2014, 103 (10), 3022−3032.
5. 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
6. Prachi Joshi and Abhay T Sangamwar. Stabilizing supersaturated drug delivery system through mechanism of nucleation and crystal growth inhibition of drugs. Ther. Deliv. 2018, 9(12), 873-885

7. Samarth S Thakore, Rahul P Gangwal, Ajit S Narang, Abhay T Sangamwar. Assessment of biopharmaceutical performance of supersaturating formulations of carbamazepine in rats using PBPK modelling. AAPS PharmSciTech 2019, 20(5), 179
8. Rodríguez-Hornedo, N., Murphy, D., Significance of controlling crystallization Mechanisms and kinetics in pharmaceutical systems. J. Pharm. Sci. 1999, 88, 651–660.
9. Box, K.J., Völgyi, G., Baka, E., Stuart, M., Takács-Novák, K., Comer, J.E.A.,. Equilibrium versus kinetic measurements of aqueous solubility, and the ability of compounds to supersaturate in solution-a validation study. J. Pharm. Sci. 2006, 95, 1298–1307.
10. Dai, W.-G., Dong, L.C., Shi, X., Nguyen, J., Evans, J., Xu, Y., Creasey, A.A., Evaluation of drug precipitation of solubility-enhancing liquid formulations using milligram quantities of a new molecular entity (NME). J. Pharm. Sci. 2007, 96, 2957–2969.
10. Morrison, J.S., Nophsker, M.J., Haskell, R.J., A combination turbidity and supernatant microplate assay to rank-order the supersaturation limits of early drug candidates. J. Pharm. Sci. 2014, 103, 3022–3032.
11. Yamashita, T., Kokubo, T., Zhao, C., Ohki, Y., Antiprecipitant screening system for basic model compounds using bio-relevant media. JALA: J. Assoc. Lab. Autom. 2010, 15, 306–312.
12. Ikjot Sodhi, Prabhakar Mallepogu, Vaibhav P Thorat, Mahesh C Kashyap, Abhay T Sangamwar. Insights on role of polymers in precipitation of celecoxib from supersaturated solutions as assessed by focused beam reflectance measurement (FBRM) Eur J Pharm Sci 2019, 137, 104983
13. Santosh Sunnam, Ikjot Sodhi, Prachi Joshi, Sanjaya K Samal, Abhay T Sangamwar**.** Correlating precipitation inhibition efficacy of Eudragit EPO and polyvinyl pyrrolidone (PVP) K30 on supersaturated solution of atorvastatin calcium with Caco-2permeability enhancement**.** J Drug Del Sci Tech 2020, 57, 101692
14. 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

15. 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
16. 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
17. 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
18. 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.
19. Abouhussein, Dalia M. N. Enhanced transdermal permeation of BCS class IV aprepitant using binary ethosome: Optimization, characterization and ex vivo permeation. Journal of Drug Delivery Science and Technology 2021, 61, 102185.
20. Kang, H. J., et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. Lancet Oncol 2015, 16(4), 385-94.
21. Liu, Jinwen, et al. Fabrication of an aprepitant nanosuspension using hydroxypropyl chitosan to increase the bioavailability. Biochemical and Biophysical Research Communications 2022, 631:72-77.
22. Nazlı, Hakan, Burcu Mesut, and Yıldız Özsoy, In Vitro Evaluation of a Solid Supersaturated Self Nanoemulsifying Drug Delivery System (Super-SNEDDS) of Aprepitant for Enhanced Solubility. Pharmaceuticals 2021, 14(11), 1089.
23. Nanaki, Stavroula, et al. 2019 Aprepitant Drug in Ternary Pharmaceutical Solid Dispersions with Soluplus® and Poloxamer 188 Prepared by Melt Mixing. Sci. 2019, 1(2), 48
24. Guan, Qingran, et al. Cellulose derivatives as effective recrystallization inhibitor for ternary ritonavir solid dispersions: In vitro-in vivo evaluation. Carbohydrate Polymers 2021, 273, 118562.

25. Prasad, Dev, Harsh Chauhan, and Eman Atef, Amorphous Stabilization and Dissolution Enhancement of Amorphous Ternary Solid Dispersions: Combination of Polymers Showing Drug–Polymer Interaction for Synergistic Effects. Journal of Pharmaceutical Sciences 2014, 103(11), 3511-3523.
26. Mukesh, Sumit, et al. Comparative analysis of drug-salt-polymer interactions by experiment and molecular simulation improves biopharmaceutical performance. Communications Chemistry 2023, 6(1), 201.