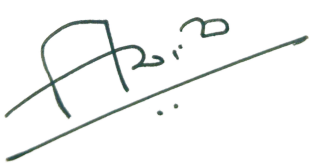
Details of Research Work

Amorphous systems

Dr. Bansal's studies have helped to develop a fundamental understanding of amorphous phases of pharmaceuticals. Thus, he has evaluated the molecular relaxation behavior and isothermal crystallization in the supercooled state. Since amorphous materials have a strong tendency to sorb water, he has investigated the effect of different states of sorbed water on the behavior of amorphous celecoxib (Shete G, Kuncham S, Puri V, Gangwal R, Sangamwar A T and Bansal A K. Effect of different 'states' of sorbed water on amorphous celecoxib. **Journal of Pharmaceutical Sciences**, 2014:103(7), 2033–2041). In addition, the effect of humidity on the alpha-relaxations of low-density polyethylene was evaluated using dielectric spectroscopy. (Amin A, Dantuluri A K and Bansal A K. Investigating the effect of humidity on the alpha-relaxations of low-density polyethylene using dielectric spectroscopy. **International Journal of Pharmaceutics**, 2012:422, 302-309). Molecular mobility in amorphous materials is also manifested as enthalpic relaxation. This was investigated in two structurally related amorphous drugs and their binary dispersions. His studies proposed the use of enthalpy relaxation studies to screen stabilizers for amorphous solid dispersions (Bansal S S, Kaushal A M and Bansal A K. Enthalpy relaxation studies of two structurally related amorphous drugs and their binary dispersions. **Drug Development and Industrial Pharmacy**, 2010:36(11), 1271-80). The determination of the glass transition temperature in freeze-concentrates can often be a challenge. Dr. Bansal has developed a novel ex-situ super-saturation technique to determine this temperature (Kumar L and Bansal A K. Determination of glass-transition of the freeze concentrate for lyophilization using novel *ex-situ* super-saturation technique. **ThermochimicaActa**, 2013:559, 82–85). He also investigated the effect of counter-ions on the glass transition temperature (Tg) during lyophilization of ganciclovir salt forms (Kumar L, Baheti A and Bansal A K. Effect of counterion on the glass transition temperature (T_g) during lyophilization of ganciclovir salt forms. **Molecular Pharmaceutics,** 2011:8(1), 309–314). In studies aimed at utilizing amorphous phases to obtain the desired biopharmaceutical properties, he investigated the solubility advantage from amorphous etoricoxib solid dispersions (Dani P, Puri V and Bansal A K. Solubility advantage from amorphous etoricoxib solid dispersions. Accepted for publication in **Drug Development and Industrial Pharmacy**, 2014: 40(1), 92-101) and the phase behavior and oral bioavailability of amorphous curcumin (Pawar Y B, Shete G, Popat D and Bansal A K. Phase behavior and oral bioavailability of amorphous curcumin. **European Journal of Pharmaceutical Sciences**, 2012:47, 56-64). One major challenge with amorphous phases is their propensity to crystallize. Therefore, strategies need to be developed to minimize the risk of crystallization. With this goal in mind, Dr. Bansal investigated the role of thermodynamic, kinetic and structural factors in the



recrystallization behavior of amorphous erythromycin salts (Nanakwani K, Modi S R and Bansal A K. Role of thermodynamic, kinetic and structural factors in the recrystallization behavior of amorphous erythromycin salts. **ThermochimicaActa,** 2014:582, 77-85).

Dr Bansal's group investigated the intermolecular interactions in the crystalline and amorphous state to understand the molecular basis of physical stability of these samples (Kaushal A, Chakraborti A K and Bansal A K. FTIR Studies on differential intermolecular association in crystalline and amorphous states of structurally related non-steroidal anti-inflammatory drugs. **Molecular Pharmaceutics**, 2008:5(6), 937–945). The present study was designed to understand the differences in intermolecular interactions in amorphous and crystalline phases in a series of structurally related compounds- celecoxib (CLB), valdecoxib (VLB), rofecoxib (RFB), and etoricoxib (ETB). Comparison of four crystalline phases though revealed significantly variations, the interactions were remarkably similar in the amorphous state, possibly as a result of constraints of crystal packing ceasing to exist. Conversion of crystalline state to amorphous state led to weakening of some interactions while others got strengthened. The differences in intermolecular interactions could successfully explain the differences in thermodynamic properties studied previously.

Amorphous solid dispersions provide a robust platform to stabilize the amorphous form and exploit their enhanced solubility. Stabilization of an amorphous solid against devitrification can be achieved using additives that interact specifically with the parent molecule, and restrain it from rearranging into a crystal lattice. The amorphous form of celecoxib (CEL) was stabilized by poly(vinylpyrrolidone) (PVP), both in the solid state and during dissolution. A comprehensive characterization of CEL-PVP binary amorphous systems by thermal, spectroscopic, and computer simulation techniques provided greater insight into the molecular interaction between the two species. The studied molecular interactions between CEL and PVP supported the stabilizing action of PVP for the amorphous form of CEL (Gupta P, Thilagavathi R, Chakraborti A K and Bansal A K. Role of molecular interaction in stability of Celecoxib-PVP amorphous systems. **Molecular Pharmaceutics,** 2005:2(5), 384-391).

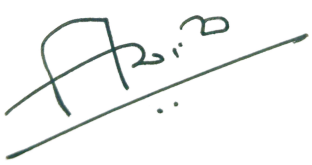
Drug-polymer miscibility is an important criteria for the stability of amorphous systems. Drug-polymer miscibility has been proposed to play a critical role in physical stability of amorphous solid dispersions (ASDs). The purpose of Dr Bansal's recent research was to investigate the role of drug-polymer miscibility on molecular mobility, measured as enthalpy relaxation (ER) of amorphous irbesartan (IBS) in ASDs. (Dalsania S, Sharma J, Munjal B, Bansal AK. Impact of drug-polymer miscibility on enthalpy relaxation of irbesartan amorphous solid dispersions. **Pharmaceutical Research**, 2018:35(2),29). A miscible drug-polymer system can help in reducing thermodynamic activity of the drug in comparison to the pure amorphous drug by affecting the

glass transition (Tg) and the melting temperature of the drug. This can be achieved by an increase in Tg of the amorphous drug and reduction of melting point, thus making thermodynamic driving force less favorable for crystallization.

Dr Bansal's group also worked on translation development of amorphous solid dispersion formulations. They developed barrier coated multi unit particulate system for to maximize solubility advantage (Puri V, Dantuluri A K and Bansal A K. Barrier coated drug layered particles for enhanced performance of amorphous solid dispersion dosage form. **Journal of Pharmaceutical Sciences**, 2011:101(1), 342-353). Surface phenomena dominated the performance of amorphous celecoxib solid dispersion (ACSD) comprising of amorphous celecoxib (A-CLB), polyvinylpyrrolidone, and meglumine (7:2:1, w/w). ACSD cohesive interfacial interactions hindered its capsule dosage form dissolution (Puri V, Dhantuluri AK, Bansal AK 2011. J Pharm Sci 100:2460-2468). Furthermore, ACSD underwent significant devitrification under environmental stress. In the present study, enthalpy relaxation studies revealed its free surface to contribute to molecular mobility. Based on all these observations, barrier coated amorphous CLB solid dispersion layered particles (ADLP) were developed by Wurster process, using microcrystalline cellulose as substrate and polyvinyl alcohol (PVA), inulin, and polyvinyl acetate phthalate (PVAP) as coating excipients.

Phase behavior of drugs during freeze concentration in the lyophilization process

Lyophilization is an important tool for formulation development and the processing of heat-labile pharmaceuticals. Dr. Bansal's group has carried out research to understand the behavior of solid forms during freeze concentration. His laboratory has evaluated the phase behavior of gemcitabin hydrochloride (GHCl) during freezing, along with the influence of selected processing and formulation variables, on their solid form behavior during lyophilization (Munjal B, Bansal AK. Impact of Tert-Butyl Alcohol on Crystallization Kinetics of Gemcitabine Hydrochloride in Frozen Aqueous Solutions. ***Journal of pharmaceutical sciences*** 2015, 104 (1): 87-97). Crystallization of GHCl in frozen solution was affected by the type and concentration of the buffering agents (Kumar, Mehul, Munjal B and Bansal A K. Differential effect of buffering agents on the crystallization of gemcitabine hydrochloride in frozen solutions. **International Journal of Pharmaceutics**, 2014:471(1-2), 56-64). The differential effect of buffering agents on GHCl crystallization was explained by consideration of two opposing factors: (i) their own crystallization tendency and (ii) unfrozen water content (UWC) in the freeze concentrate. Similarly, the effect of bulking agents, including sugars, was investigated. Non-crystallizing sugars inhibited GHCl crystallization in a concentration-dependent manner. However, the observed inhibitory effect of sugars could not be described by their anti-plasticization effect. This counter-intuitive behavior was rather explained by the inhibitory effect of sugars on ice



crystallization, which increased the UWC in the freeze concentrate, thereby lowering the supersaturation of GHCl. Thus, the importance of the impact of unfrozen water on governing the crystallization behavior of solutes in multi-component frozen systems was highlighted. Lyophilization often involves the salt form of the drugs, and Dr. Bansal's group also investigated the effect of the counter-ion of the salt form on lyophilization (Kumar L and Bansal A K. Effect of counterion on the phase behaviour during lyophilization of indomethacin salt forms. **European Journal of Pharmaceutical Sciences**, 2011:44, 136-141 and Kumar L, Baheti A and Bansal A K. Effect of counterion on the glass transition temperature (T_g) during lyophilization of ganciclovir salt forms. **Molecular Pharmaceutics,** 2011:8(1), 309–314).

Their group investigated the phase behavior of cyclophosphamide (CPA) during various stages of lyophilization, with special emphasis on obtaining crystalline CPA monohydrate (CPA-MH) in the lyophilized product. Subambient differential scanning calorimetry and low-temperature X-ray diffractometry (LTXRD) were used to study the phase behavior of CPA solution (3.7% w/v). *In situ* lyophilization in LTXRD chamber was used to monitor the phase transitions occurring during the drying stages.This study highlights the relationship of process parameters used during lyophilization with the solid form of lyophilized CPA (Munjal B, Zode SS, Bansal AK. Crystallization of Cyclophosphamide Monohydrate during Lyophilization. **Journal of Pharmaceutical Sciences**, 2019, 108 (3), 1195-1202).

Mannitol is a commonly used bulking agent in lyophilized formulations. It can crystallize into multiple solid forms during lyophilization thereby exhibiting phase heterogeneity and variability in product performance. In this manuscript, we studied the effect of cyclophosphamide (CPA), an anticancer drug, on the solid form of mannitol during lyophilization from aqueous solutions. Freeze-concentration studies were performed in the DSC while lyophilization was performed in a lab scale freeze dryer (Patel K, Munjal B and Bansal AK. Effect of cyclophosphamide on the solid form of mannitol during lyophilisation, accepted for publication in **European Journal of Pharmaceutical Sciences** in February 2017)

Molecular understanding of compaction behavior of pharmaceutical solids

Dr. Bansal's group has worked extensively in the area of the compaction behavior of pharmaceuticals. They investigated the effect of the molecular and particle level material properties, and process parameters, including compaction force, compaction speed and roller pressure, on the compaction properties of pharmaceutical powders. Using polymorphs of different APIs, including clopidogrel bisulfate (Khomane K, More P and Bansal A K.Counterintuitive compaction behavior of clopidogrel bisulfate polymorphs.**Journal of Pharmaceutical Sciences**, 2012:101, 2408-2416), indomethacin (Khomane K S, More P K,

Raghavendra G and Bansal A K. Molecular understanding of the compaction behaviour of indomethacin polymorphs. **Molecular Pharmaceutics,**2013:10, 631–639) and ranitidine hydrochloride (Upadhyay P, Khomane K S, Kumar L, Bansal A K. Relationship between crystal structure and mechanical properties of ranitidine hydrochloride polymorphs. **Crystal Engineering Communication,** 2013:15, 3959–3964), they established a novel relationship between crystal packing density (true density) and the bonding strength of compacted pharmaceuticals. Compaction behavior was also investigated vis-à-vis the role of weak hydrogen bonding on active slip systems (Khomane K S and Bansal A K. Weak hydrogen bonding interactions influence slip system activity and compaction behavior of pharmaceutical powders. **Journal of Pharmaceutical Sciences**, 2013:102(12), 4242-4245) and particle size (Khomane K S and Bansal A K. Effect of particle size on in-die and out-of-die compaction behaviour of ranitidine hydrochloride polymorphs. **AAPS Pharmaceutical Science and Technology**, 2013:14,1169-1177). Dry granulation exposes the material to two compaction cycles and can influence tableting. The role of size enlargement and hardening of granules was investigated (Patel S, Dahiya S K, Sun C and Bansal A K. Understanding size enlargement and hardening of granules on tabletability of unlubricated granules prepared by dry granulation. **Journal of Pharmaceutical Sciences,** 2011:100(1), 758–766). The Heckel parameter is very commonly used to characterize the compaction behavior, and Dr. Bansal's group studied the pressure dependency of the Heckel parameter (Patel, S. Kaushal A M and Bansal A K. Mechanistic investigation on pressure dependency of Heckel parameter. **International Journal of Pharmaceutics,** 2010:389, 66–73). Additional studies on the compaction behavior of a eutectic mixture (Jain H K, Kailas K and Bansal A K. Implication of microstructure on the mechanical behaviour of an aspirin–paracetamol eutectic mixture. **Crystal Engineering Communication,** 2014:16, 8471-8478) and that of drugs coated with ultrafine particles (More P, Khomane K S and Bansal A K. Flow and compaction behaviour of ultrafine coated ibuprofen. Accepted for publication in **International Journal of Pharmaceutics**, 2013:441, 527–534) have provided practical information on compaction behavior.

In an interesting publication entitled "Single-Crystal Plasticity Defies Bulk-Phase Mechanics in Isoniazid Cocrystals with Analogous Coformers", the crystal structures of four INZ cocrystals with analogous crystal coformers were probed to understand the relationships among molecular packing, H-bonding dimensionality, single-crystal plasticity, and bulk mechanical behavior. A gross deviation was observed between single crystal mechanics and bulk level compaction behavior. Therefore, nanomechanical attributes are more predictive of more isotropic molecular crystals, such as 3D H-bonded or interlocked structures, in comparison to those exhibiting gross structural anisotropy, such as crystals with distinct molecular layers that favor facile slip. Hence, the accurate prediction of bulk behavior on the basis ofnanomechanical characterization requires the incorporation of crystal shape and packing as well as knowledge

of facet-specific mechanical properties (Yadav JP, Yadav RN, Sihota P, Chen H, Wang C, Sun CC, Kumar N and Bansal AK. Single crystal plasticity defies bulk-phase mechanics in Isoniazid cocrystals with analogous coformers. **Crystal Growth & Design**, 2019, 19(8), 4465-4475).

In a rapid communication entitled "Weak Hydrogen Bonding Interactions Influence Slip System Activity and Compaction Behavior of Pharmaceutical Powders" in Journal of Pharmaceutical Sciences, Dr. Bansal's research highlighted that presence of slip planes in the crystal lattice allows easier slip under the applied compaction pressure. This allows greater plastic deformation of the powder and results into increased interparticulate bonding area and greater tensile strength of the compacts. A case study was reported where larger numbers of C–H···O type interactions across the proposed slip planes hinder the slip and thus resist plastic deformation of the powder under the applied compaction pressure. Hence, attention must be given to these types of interactions while identifying slip planes by visualization method. Generally, slip planes are visualized as flat layers often strengthened by a two-dimensional hydrogen-bonding network within the layers or planes. No hydrogen bonding should exist between these layers to consider them as slip planes. Moreover, one should also check the presence of C–H···O type interactions across these planes. This provided a new perspective for molecular understanding of compaction behavior of pharmaceuticals. (Khomane K S and Bansal A K. Weak hydrogen bonding interactions influence slip system activity and compaction behavior of pharmaceutical powders. **Journal of Pharmaceutical Sciences**, 2013:102(12), 4242-4245)

Febuxostat exists in multiple polymorphic forms and offers an opportunity to understand structure property relationship. Febuxostat Form Q (FXT Q) and Form H1 (FXT H1) were investigated for crystal structure, nanomechanical parameters, and bulk deformation behavior. This study supported how molecular level crystal structure confers a bridge between particle level nanomechanical parameters and bulk level deformation behavior (Yadav JP, Khomane K, Modi S, Ugale B, Yadav RN, Nagaraja CM, Kumar N, and Bansal, AK. Correlating Single Crystal Structure, and Nanomechanical and Bulk Compaction Behavior of Febuxostat Polymorphs, accepted for publication in **Molecular Pharmaceutics,**2017, 14, 3, 866–874).

Crystal habit and biopharmaceutical performance of BCS class II drugs

Dr. Bansal's research has provided novel and interesting insights into the effect of crystal habit on intrinsic dissolution (13), solubility and bioavailability of BCS class II drugs. The effect of crystal habit on compaction behavior was also demonstrated. Hence, they established a molecule-centered approach towards crystal habit modification of a BCS class II drug, celecoxib (CEL), and its effect on solubility, dissolution behavior, oral bioavailability, and overall

pharmaceutical product performance. This study has also provided a mechanistic understanding of a differential-surface molecular environment, contributed by the differential exposure of crystalline facets and its impact on pharmaceutical product performance. This work mandates considering crystal habit as a 'critical material attribute' in the QbD of oral solid dosage forms of BCS class II drugs (Modi, S. R.; Dantuluri, A. K.; Perumalla, S. R.; Sun, C. C.; Bansal, A. K. Effect of crystal habit on intrinsic dissolution behavior of celecoxib due to differential wettability. **Crystal Growth Design,** 2014: 14, 5283-5292).

In a study published from their lab (Jain T, Sheokand S and Bansal AK. Effect of differential surface anisotropy on performance of two plate shaped crystals of aspirin form I. **European Journal of Pharmaceutical Sciences**,Volume 99, March 2017, Pages 318–327), they investigated the impact of differential surface anisotropy of two plate-shaped crystals of aspirin (form I) on their hygroscopicity, stability and compaction behavior. These crystals differed in their predominant facets (100) and (001). (100) facets exposed polar carbonyl groups which provided hydrophilicity to the facets. In contrast, (001) facets possessed hydrophobicity as they exposed non-polar aryl and methyl groups. Both the samples showed different degradation behavior, at various stability conditions (i.e. 40°C/75%RH, 30°C/90%RH and 30°C/60%RH) and different time intervals.

Nanocrystalline solid dispersions

Dr. Bansal's group has developed a novel 'bottoms-up' platform technology for the generation of nanocrystalline solid dispersionsShete GB and Bansal AK. "NanoCrySP Technology for Generation of Drug Nanocrystals: Translational Aspects and Business Potential", **Drug Delivery and Translational Research**, February 2016 (DOI: 10.1007/s13346-016-0286-y). They have demonstrated the biopharmaceutical benefits of this technology. Their group has also established the contribution of molecular mobility, heterogeneous nucleation (Bhatt V, Shete GB and Bansal AK. Mechanism of Generation of Drug Nanocrystals in Celecoxib : Mannitol Nanocrystalline Solid Dispersion. **International Journal of Pharmaceutics**2015, 495 (1): 132-139), and the effect of excipients on nucleation & crystal growth, in the formation of nanocrystalline solid dispersions (Shete GB, Modi SR and Bansal AK. Effect of Mannitol on Nucleation and Crystal Growth of Amorphous Flavonoids: Implications on the Formation of Nanocrystalline Solid Dispersion. **Journal of Pharmaceutical Sciences**, 2015 Jul 16. doi: 10.1002/jps.24586).

The nano crystalline solid dispersions were demonstrated to form through intermediate amorphous state. Crystallization inducing excipients used, modulated the nucleation and crystal growth of the drugs and led to formation of nano crystals. Dr Bansal's group studied crystallization kinetics of amorphous hesperetin (HRN) and naringenin (NRN) alone, and in 1:1

proportion with mannitol at Tg + 15 K. Crystallization rate of NRN was found to be significantly higher than HRN. Mannitol accelerated crystallization of HRN as well as NRN. NRN exhibited higher crystallization rate than HRN, in presence of mannitol, as well. Finke-Watzky model was used to deconvolute the crystallization kinetics data into nucleation and crystal growth rate constant. HRN alone had 9.56 × 109 times faster nucleation rate and 1.88 times slower crystal growth than NRN alone. Mannitol increased nucleation and crystal growth rate of HRN as well as NRN. In presence of mannitol, HRN possessed 1.34 × 1010 times faster nucleation rate and 1.70 times slower crystal growth rate than NRN. Differences in crystallization behavior of HRN and NRN were explained by their thermodynamic properties (Shete GB, Modi SR and Bansal AK. Effect of Mannitol on Nucleation and Crystal Growth of Amorphous Flavonoids: Implications on the Formation of Nanocrystalline Solid Dispersion. **Journal of Pharmaceutical Sciences**, 2015 Jul 16. doi: 10.1002/jps.24586).

They studied the role of formulation and process parameters on solution- and solid-state crystallization kinetics of fenofibrate (FNT) to attain its submicron crystallite size in spray-dried solid dispersion. Crystallization kinetics of FNT in the solution-state was affected by the degree of supersaturation achieved as a function of temperature and excipients. The nucleation induction time of FNT was significantly reduced in the presence of mannitol (MAN), sodium lauryl sulfate (SLS), and dioctyl sulfosuccinate sodium (DOSS). The surfactants (SLS and DOSS) and matrix former (MAN) affected solution- and solid-state crystallization kinetics of FNT, respectively. This study has important implications in the rational designing of nanocrystalline solid dispersions of FNT using bottom-up approaches like NanoCrySP (Thakur PS, Sheokand S, Bansal AK. Factors Affecting Crystallization Kinetics of Fenofibrate and Its Implications for the Generation of Nanocrystalline Solid Dispersions via Spray Drying. **Crystal Growth & Design**, 2019, 19 (8), 4417-4428).

The platform technology developed in Dr Bansal's lab, was investigated for its use in development of ophthalmic suspension formulation (9). Prednisolone Acetate (PAC) is currently marketed as micronized ophthalmic suspension. The microsuspension has poor dose accuracy and efficacy due to aggregation, slow dissolution rate and limited corneal residence. The ophthalmic nanosuspension of PAC shall show enhanced solubility, dissolution rate and corneal adhesion due to small particle size and increased surface area. His research group prepared ophthalmic formulation of PAC using a novel, spray drying based technology. Firstly, PAC nanocrystalline solid dispersions (NCSD) were prepared using Mannitol (MAN) as the crystallization inducing excipient and two separate stabilizers, Polyvinyl Alcohol (PAC_MAN_PVA) and Vitamin E Tocopheryl Polyethylene Glycol Sulphosuccinate (PAC_MAN_TPGS). The NCSD was dispersed in an aqueous vehicle to obtain an ophthalmic nanosuspension (Nandwani Y, Kaur A

and Bansal AK. Generation of Ophthalmic Nanosuspension of Prednisolone Acetate Using a Novel Technology, **Pharm Res**, 2021 Feb;38(2):319-333).

In comparison to the existing techniques for generation of nanocrystals, NanoCrySP technology significantly reduces the downstream processing and simplifies development of final dosage form. They compared downstream processing of NS and NCSD of diclofenac acid (DCF) prepared by wet media milling and NanoCrySP technology, respectively. The NS and NCSD were characterized for crystallinity, crystal size, assay and dissolution.The overall cost for downstream processing of NCSD was up to 80% lower than that of NS. An innovation radar tool also concluded that the one-step NanoCrySP technology was more efficient and required less downstream processing than the two-step wet media milling approach for conversion of nanocrystals to OSD (Jadhav S, Kaur A, Bansal AK. Comparison of Downstream Processing of Nanocrystalline Solid Dispersion and Nanosuspension of Diclofenac Acid to Develop Solid Oral Dosage Form,**Pharmaceutics 2020**, *12*(11), 1015).

Determination of API particle size is challenging in NanoCrySP generated NCSD, as the nanocrystals are embedded in the matrix of the excipient. (20) Firstly, neat CEL_NCSD was analyzed using Scherrer equation. Secondly, MAN was dissolved in an aqueous stabilizer medium to selectively measure the size of CEL nanocrystals. Raman Spectra captured in Morphologi G3-ID confirmed the presence of CEL-only particles in the media. Thus, the study revealed that optimized sample preparation is critical for the size determination of embedded drug nanocrystals in NCSD (Kaur A, Parmar PK, and Bansal AK. Evaluation of Different Techniques for Size Determination of Drug Nanocrystals: A Case Study of Celecoxib Nanocrystalline Solid Dispersion. **Pharmaceutics**, 11 (10), 516).

NanoCrySP technology was also evaluated for generation of nano crystalline solid dispersion of combination drugs. (21). Dual drug nanocrystals loaded nano embedded microparticles (DNEMs) were prepared for fixed dose combination of simvastatin (SIM) and ezetimibe (EZE) using NanoCrySP technology. The purpose was to generate nanonized SIM and EZE dispersed in matrix of single crystallization inducing excipient and investigate their *in vitro* performance. Powder dissolution of DNEM increased 1.45 times for SIM and 1.65 times for EZE as compared to their physical mixture in discriminatory medium. MAN did not plasticize SIM or EZE by virtue of its immiscibility with the two drugs. However, MAN helped in inducing crystallization via heterogeneous nucleation. The generated DNEM were stable in terms of assay, polymorphic form and dissolution for 90 days of accelerated storage at 40 °C/75% RH (Nandi S, Kaur A and Bansal AK. Dual Drug Nanocrystals loaded Microparticles for Fixed Dose Combination of Simvastatin and Ezetimibe. **Pharmaceutical Development and Technology**2020 Jan;25(1):40-53).

Co crystals

The last 2 decades have witnessed increased research in the area of cocrystals resulting in deeper scientific understanding, increase in intellectual property landscape, and evolution in the regulatory environment. Pharmaceutical cocrystals have received significant attention as a new solid form on account of their ability to modulate poor physicochemical properties of drug molecules. Dr Bansal's group has been working at the interface of crystal engineering and formulation development to enhance scientific understanding behind use of co crystals as alternate solid forms. In a commentary published in Journal of Pharmaceutical Sciences (Kale D, Zode S and Bansal AK. Challenges in Translational Development of Pharmaceutical Cocrystals. Accepted for publication in **Journal of Pharmaceutical Sciences**, 2017, 106 (2), February 2017, 457–470), the role of cocrystals in the modulation of material properties and challenges involved in the pharmaceutical development of cocrystals were discussed. The major hurdles encountered in the development of cocrystals such as safety of coformers, unpredictable performance during dissolution and solubility in different media, difficulties in establishing in vitro-in vivo correlation, and polymorphism were extensively discussed. The influence of selecting appropriate formulation and process design on these challenges was also discussed.

Dr Bansal's group also worked on understanding molecular basis of pharmaceutical behavior of cocrystals. They investigated the molecular basis of water sorption behavior of rivaroxaban-malonic acid cocrystal (RIV-MAL). It was hypothesized, that the amount of water sorbed by a crystalline solid is governed by the surface molecular environment of different crystal facets and their relative abundance to crystal surface. Water sorption behavior was measured using a dynamic vapor sorption analyzer. The surface molecular environment of different crystal facets and their relative contribution were determined using single crystal structure evaluation and face indexation analysis, respectively. The study highlighteds that the amount of water sorbed by the cocrystalis governed by the surface molecular environment and additionally by the strength of hydrogen bonding. This investigation has implications on designing materials with a desired moisture-sorption property (Kale DP, PV Bharatam, CM Nagaraja, G Dubey, B Ugale and Bansal AK. Molecular basis of water sorption behavior of rivaroxaban-malonic acid cocrystal. **Molecular Pharmaceutics**, 2019, 16(7), 2980-2981).

Co-crystals can also modulate the compaction behavior of the APIs. Research was carried out to understand the crystallographic basis of the mechanical behavior of rivaroxaban-malonic acid cocrystal (RIV-MAL Co) in comparison to its parent constituents, i.e., rivaroxaban (RIV) and malonic acid (MAL). The mechanical behavior was evaluated at the bulk level by performing "out of die" bulk compaction and at the particle level by nanoindentation. Interestingly, a

particle level deformation parameter H/E (i.e., ratio of mechanical hardness H to elastic modulus E) was found to inversely correlate with a bulk level deformation parameter σ0 (i.e., tensile strength at zero porosity). The present study highlighted the role of cocrystal crystallographic properties in improving the tabletability of materials (Kale DP, Puri V, Kumar A, N Kumar and Bansal AK, The Role of Cocrystallization-Mediated Altered Crystallographic Properties on the Tabletability of Rivaroxaban and Malonic Acid, **Pharmaceutics** 12 (6), 546).

Scale up of cocrystals offers challenge from a process chemistry perspective. Dr Bansal's group evaluated use of spray drying for generation of the cocrystals. Carbamazepine–Nicotinamide cocrystal (CNC) was chosen as model cocrystal system for this study. Firstly, CNC was generated using liquid assisted grinding and used for generation of phase solubility diagram (PSD) and ternary phase diagram (TPD). Both PSD and TPD were carefully evaluated for phase behavior of CNC when equilibrated with solvent. The undersaturated region with respect to CNC, as depicted by TPD, was selected as target region to initiate cocrystallization experiments. It was demonstrated that spray drying, owing to its simplicity and industrial scalability, can be a promising method for large scale cocrystal generation (Patil S P, Modi S R and Bansal A K. Generation of 1:1 Carbamazepine: Nicotinamide cocrystals by spray drying. **European Journal of Pharmaceutical Sciences,** 2014:62, 251-257).

Improved Delivery of Curcumin

Curcumin, derived from turmeric, has intrigued biologists and drug delivery scientists. It offers extensive pharmacological properties but its use as a therapeutic agent is complicated by its poor aqueous solubility and extensive metabolism, that limits its oral bioavailability. Dr Bansal's group worked on this challenging problem to improve the oral bioavailability of curcumin.

They investigated the reasons behind poor oral bioavailability of curcumin (Wahlang B, Pawar Y B and Bansal A K. Identification of permeability-related hurdles in oral delivery of curcumin using Caco-2 cell model. **European Journal of Pharmaceutics and Biopharmaceutics,** 2011:77, 275–282). Poor aqueous solubility and extensive metabolism have been implicated for this but the role of membrane permeability has not been investigated. In the present study, permeability of curcumin was assessed using the Caco-2 cell line. Curcumin was poorly permeable with a P(app) (A → B) value of 2.93 ± 0.94 × 10(-6)cm/s. P(app) value in (B → A) study was found out to be 2.55 ± 0.02 × 10(-6)cm/s, thus ruling out the role of efflux pathways in poor oral bioavailability of curcumin.Curcumin was also found to accumulate in cells as revealed by CLSM studies.Thus, intestinal first-pass metabolism and intracellular accumulation played a role in poor permeability of curcumin. Based on its poor aqueous solubility and intestinal permeability, curcumin can be classified as a BCS Class IV molecule. This information

can facilitate designing of drug delivery systems for enhancement of oral bioavailability of curcumin.

In another study various types of delivery systems of curcumin were compared for oral bioavailability (Munjal B, Pawar Y and Bansal A K. Comparative oral bioavailability advantage from curcumin formulations. **Drug Delivery and Translational Research,**2011:1(4), 322-331). oral bioavailability of seven different formulations of curcumin (CRM). CRM formulations viz. aqueous suspension, micronized suspension, nanosuspension, amorphous solid dispersion, hydroxypropyl-β-cyclodextrin (HP-β-CD) inclusion complex, combination with piperine, and spray-dried CRM-milk composite were compared for oral bioavailability in male Sprague-Dawley rats.

Dr Bansal's group investigated the role of formulation excipients in enhancing permeation of curcumin (Wahlang B, Pawar Y B, Kabra D, Tikoo K B and Bansal A K. Contribution of formulation and excipients towards enhanced permeation of curcumin**. Arznemittelforschung Drug Research**, 2012:62, 88-93). A self nano-emulsifying drug delivery system (CRM SNEDDS) consisting of Labrasol, Gelucire 44/14, Vitamin E TPGS and PEG 400 was designed and provided 16 times improvement in oral bioavailability in rats, at a dose of 250 mg/kg body weight. Similarly oral bioavailability of amorphous curcumin was also investigated (Pawar Y B, Shete G, Popat D and Bansal A K. Phase behavior and oral bioavailability of amorphous curcumin. **European Journal of Pharmaceutical Sciences**, 2012:47, 56-64). Novel lipid based formulations were developed to significantly enhance the oral bioavailability of curcumin (Pawar Y B and Bansal A K. Novel lipid based oral formulation of curcumin: Development and optimization by Design of Experiments approach. **International Journal of Pharmaceutics**, 2012:436, 617–623).

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