Statement of Research Achievements on Which Fellowship has already been Received

Prof. Abhay is a recipient of prestigious German Academic Exchange Service-DAAD Fellowship on the project under Indo-German cooperation in health research

The drug delivery laboratory (DDL) led by Prof. Abhay belongs to NIPER, SAS Nagar. NIPER is an institute of National Importance under the aegis of Ministry of Chemicals and Fertilizers, Department of Pharmaceuticals, New Delhi. DDL show long expertise in supersaturable solid and lipid drug delivery systems for enhancement of biopharmaceutical performance of drugs. The research group has strong skills in the development of supersaturation assays (in vitro) of drugs, amorphous drug formulations and new supersaturable lipid drug delivery systems for difficult to absorb drugs. Prof. Abhay is working in the development of novel vision of rational drug design based on a multiphysics approach for discovery, design and optimizes selective, potent and safe drug candidates and further tested in vitro and in vivo. Abhay's group has a strong connection with several pharmaceutical companies in projects focused on rational drug delivery design and optimization. Particularly, computational analysis were requested to reach several challenges, such as, the characterization of: 1) physic-chemical drug behaviour (e.g aggregation) at different condition (pH, temperature, pressure), *ii)* drug interaction with biological structures (e.g. cellular membrane), iii) drug diffusion through membrane, iv) target proteins (e.g. structure and behaviour modelling), v) target-compound interaction (e.g. binding affinity and mode) and dynamics (local and global motion of the target, dimerization, differences between activator-inhibitory effects), vi) prediction of new chemicals activity (QSAR) and PK and toxicity profile (ADME-T).

In a recent study Prof Abhay's group employed coarse grained molecular dynamics (Martini Force field) in collaboration with Prof Rebecca Wade from Heidelberg University, Germany. This study is supported by experimental techniques to characterise the celecoxib-celecoxib molecular level self-assembly I neutral and ionized form. In more detail, we described a comparative experimental and computational characterization of amorphous solid dispersions containing the drug celecoxib and a polymer. Classical models for drug polymer interactions fail to identify the best drug salt. Prof. Abhay's long collaboration with Prof Rebecca has turned into a project under Indo-German cooperation in health research. The project entitled 'Investigation of drug-polymer interactions by coarse grained molecular dynamics simulation for stable drug formulations' was designed with the objectives of development of force field parameters for polymer and drug, development of solid dispersion with selected grade of polymer (obtained from in silico study) and drug, in vitro and in vivo evaluation of the optimized drug delivery system.

This collaboration and fellowship has an excellent outcome in terms of one Indian patent and research paper at Nature-Communications Chemistry.

Patent

Novel Amorphous Pharmaceutical Formulations of Celecoxib Salts in Polymeric Solid Dispersion with Improved Aqueous Solubility and Stability

Indian Patent Application Number-202011007741

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Research Paper

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

Brief Citation on the Research Work

Many pharmaceutical drugs are poorly water-soluble, and this property hinders their ability to reach the systemic circulation in the required concentration for optimal therapeutic effect. To overcome this problem, such drugs can be formulated in a high-energy amorphous solid state. This allows attainment of supersaturation exceeding the equilibrium solubility of the drug and thereby increases the flux across biological membranes [1]. However, the supersaturated state of drug molecules is metastable and therefore the drug molecules tend to aggregate and recrystallize, adversely affecting the biopharmaceutical properties of the drug [2]. In a typical pipeline to select excipients, such as polymers[3], lipids[4] or surfactants[5], to attain supersaturation of a poorly water-soluble drug (PWSD) and thereby enhance bioavailability, various supersaturated drug delivery systems are explored. A better understanding of the determinants of drug-drug and drug-excipient interactions and their relation to drug bioavailability would allow a more rational choice of drug-excipient combinations. Towards this goal, we describe a comparative computational and experimental investigation of polymeric excipients for celecoxib (CEL), a selective COX-2 inhibitor that is a PWSD. CEL is widely used for treating inflammatory diseases, including rheumatoid arthritis, osteoarthritis and ankylosing spondylitis,[6] and hence a formulation with better solubility and bioavailability would be of enormous therapeutic benefit.

The global CEL market was valued at 1149.8 million USD in 2020 and is expected to reach 1606.1 million USD by the end of 2026, growing at a CAGR (compound annual growth rate) of 8.7% from 2021 to 2026[7]. The global CEL market is mostly dominated by Pfizer, which markets CELEBREX®. CELEBREX® contains micronized CEL particles, sodium croscarmellose as a disintegrant, and povidone K30 and sodium lauryl sulphate (SLS) as solubilizers, for enhancing the solubility and oral bioavailability of CEL [8]. However, SLS is an anionic surfactant that causes strong mucosal irritation and structural modification to proteins and phospholipids, leading to toxicity in humans [9]. Moreover, the positive food effect observed for CELEBREX® results in varying levels of absorption of CEL. Intake of CELEBREX® is recommended with food to improve absorption, but due to differences in food intake and diet, interpatient variability in the pharmacokinetic parameters can impede correct dosing [10]. Furthermore, treatment requires the administration of high doses of CEL, generally 200-400 mg twice daily for a prolonged period for treating serious conditions, which can lead to adverse events, such as hypersensitivity reactions (anaphylaxis), abdominal

pain, nasopharyngitis and arthralgia, that hamper therapy[11]. Thus, there is an unmet need for the development of improved dosage formulations for CEL.

We previously found that supersaturated amorphous drug-salt-polymer systems, termed amorphous salt solid dispersions (ASSD), are better than conventional binary amorphous solid dispersions (ASD) in enhancing the aqueous solubility, physical stability and bioavailability of CEL[12]. Specifically, ASSDs generated using *in situ* salt formation of CEL, which has a pK_a of 11.1, with Na^+ and K^+ counterions in the matrix of a Soluplus polymer exhibited the combined effects of solubility enhancement, stabilisation through ionic interactions between drug and counterions, and intermolecular interactions between drug and polymer, that maintain the supersaturation for prolonged times in the gastrointestinal tract (GIT)[12]. Such prolonged effects offer the prospect of lowering the dose and for once-a-day administration that together would enhance patient compliance and reduce toxicity. These findings encouraged us to investigate in the present study whether other polymers, specifically polyvinylpyrrolidone vinyl acetate 64 (PVP-VA 6:4) and hydroxypropyl methylcellulose acetate succinate (HPMCAS) might have improved effects when used with Na^+ and K^+ salts of CEL in ASSDs.

It is known that intermolecular drug-polymer interactions can significantly impact the biopharmaceutical performance[13] and physical stability[14] of a drug. Indeed, the general rationale for experimental screening of polymers to identify excipients for a particular drug is to identify thermodynamically miscible systems that possess adhesive interactions (specific hydrogen bonding, hydrophobic or van der Waals interactions), between the drug and the polymer in order to hinder drug-drug aggregation[15], and thereby prevent nucleation and crystal growth in the supersaturated solution during dissolution. The traditional methods to predict drug-polymer miscibility involve the calculation of solubility parameters and Flory-Huggins (F-H) interaction parameters [16]. We first applied these methods to compute solubility parameters to assess CEL-polymer miscibility for HPMCAS and PVP-VA. However, the results obtained did not correlate well with the measured physicochemical and biopharmaceutical attributes of the amorphous formulations. Therefore, we employed molecular dynamics (MD) simulations to evaluate drug-polymer interactions.

Recent studies have employed a combination of molecular docking and MD simulations [17] or MD simulations alone to investigate interactions between drugs and excipients. Moreover, in addition to atomistic MD simulations, coarse-grained MD simulations have been carried out to understand the mechanisms of inhibition of drug-drug aggregation in the presence of an excipient. Recently, Ouyang and colleagues developed machine learning methods to aid the selection of stable drug-polymer complexes for solid dispersion formulations and their evaluation by enthalpy calculations. However, none of these studies estimated the strength of drug-drug interactions in the presence and absence of polymer, or in the presence of ions. Although molecular level mechanistic studies to elucidate the drug-polymer interplay in both solution and solid state have been performed using high-end analytical techniques, the intermolecular interactions in an aqueous environment that correlate with the *in vivo* fate of a

drug remain largely unexplored, but are particularly amenable to investigation by MD simulation.

MD simulations of neutral and anionic forms of CEL with different polymers, in aqueous solution, representing the *in vivo* environment, were performed, and compared with experimental measurements for novel supersaturated ASSDs that have the potential to address the aforementioned problems of drug-drug aggregation and crystallization. We find that hindrance of drug aggregation is attributable to stronger drug-polymer interactions in the ionized drug state in ASSDs compared to the non-ionized drug in conventional ASDs. Of the systems studied, the simulations reveal the most stable intermolecular interactions between anionic CEL and PVP-VA, correlating with experimental observations which show prolonged stability along with ameliorated dissolution and pharmacokinetic profiles, offering the prospect of less frequent administration and lower doses with cost-effectiveness and fewer side effects.

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