# ABSTRACT

**Title of Document:** CRYSTAL ENGINEERING OF POORLY WATER-SOLUBLE DRUGS

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Several Active Pharmaceutical Ingredient (API) molecules in spite of having good medicinal properties and therapeutic ability are restricted for human administration because of their hydrophobic nature. Biopharmaceutics Classification System (BCS) of drugs have classified such hydrophobic drugs with poor aqueous solubility as BCS class II drugs (drugs with poor aqueous solubility but good membrane permeability) and class IV drugs (drugs with poor aqueous solubility as well as membrane permeability).

Cocrystallization is a crystal engineering approach which can be used to fine-tune the solubility nature of such poorly water-soluble drugs through introduction of non-covalent intermolecular interactions between drug and coformer molecules. The aim of this thesis is mainly focused on cocrystal formation of a BCS class IV drug, Curcumin (CUR) and BCS class II drugs, Nevirapine (NEV) and Carbamazepine (CBZ) for enhanced dissolution and bioavailability.

CUR was observed to form cocrystal with hydroxyquinol (HXQ) and trimesic acid (TMA). CUR formed eutectics with salicylic acid (SAA), biotin (BIO), carbamazepine (CBZ), N-acetyl D,L-Tryptophan (N-ATP), paracetamol (PAR), tyrosine (TYR), glycine (GLY), succinic acid (SUC), ethyl paaraben (ETP). With IBU, CUR remained as a physical mixture. CUR-HXQ (1:2) cocrystal showed highest dissolution, about 3 times and CUR-TMA (1:1) cocrystal exhibited 1.8 times higher than raw CUR in 40% ethanol-water (v/v ratio) at 37 °C. Further CUR-SUC (1:1) eutectic exhibited 4.84 times higher dissolution compared to raw CUR in 20% ethanol-water (v/v ratio) at 37 °C.

Multicomponent crystalline solid forms of NEV (a BCS class II anti-retroviral drug) have been prepared with paracetamol (PAR), trimesic acid (TMA) and trimellitic anhydride (TMEA) as coformers. NEV formed an eutectic with PAR at NEV-PAR stoichiometric ratio of 1:3. Evaporative crystallization and slurry conversion of NEV-TMA (1:1) yielded NEV-TMA (1:1) cocrystal methanol solvate. Interestingly, TMEA underwent conversion into trimellitic acetate (TMEA acetate) on its reaction with methanol during evaporative crystallization, resulting into NEV-TMEA acetate (1:1) cocrystal hydrate. NEV-PAR (1:3) eutectic and NEV-TMA (1:1) cocrystal methanol solvate exhibited 3 times and 2

times enhanced dissolution than raw NEV in deionized water (containing 0.1 wt % SDS) dissolution medium at 37 °C.

Apart from CUR and NEV, CBZ was chosen to investigate the role of cocrystallization in enhancing dissolution of drugs with poor aqueous solubility since it has been widely explored by researchers as a model drug in crystal engineering. In case of CBZ, efforts were made to enhance dissolution of CBZ by cocrystallizing CBZ with amide, acid and hydrazide coformer molecules possessing good aqueous solubility. CBZ was observed to form cocrystal with *para*-hydroxybenzamide (PHBAD) and acetamide (ACE) by solid-state grinding, evaporative crystallization, slurry conversion and slow cooling crystallization. Interestingly, slow cooling crystallization of CBZ-ACE mixtures at stoichiometric ratios of 1:1 and 2:1 yieded CBZ dihydrate rather than cocrystals. The coformers salicylamide (SAL), pyrazinamide (PRZ), pimelic acid (PMA), suberic acid (SBA), azelaic acid (AZA), sebacic acid (SEA), isoniazid (ISN) and nicotinic acid hydrazide (NAH) formed eutectics because of the existence of weaker adhesive interaction between CBZ and the coformers. On the other hand, CBZ-maleic acid hydrazide (MAH) combination existed as a physical mixture symbolizing the absence of stronger non-covalent intermolecular interaction between CBZ and MAH. CBZ-PHBAD (1:1) cocrystals showed 8.73 times while CBZ-ACE (1:2) cocrystals displayed 7.47 times higher dissolution than raw CBZ. Among the various CBZ eutectics synthesized, CBZ-NAH (1:2) eutectic exhibited 4.93 times higher dissolution than raw CBZ in Phosphate Buffer Saline (PBS) at 37 °C.

The ultimate goal of cocrystallization was to enhance the bioavailability of NEV, CBZ and CUR. Therefore, to test the efficacy of the multicomponent solids prepared in this work, the anti-cancer and anti-invasion activity of some of the CUR multicomponent solids was evaluated against the 2D monolayers and 3D tumor models of MDA-MB-231 cells. The cytotoxicity and internalization assays conducted on 2D monolayers indicated that all CUR multicomponent solid forms except Curcumin-Folic Acid Dihydrate (CUR-FAD) (1:1) coamorphous solid exhibited enhanced bioavailability than raw CUR. Cell invasion assay conducted on 3D tumor spheroid models showed that CUR-HXQ (1:1) cocrystal completely inhibited cell invasion whereas CUR-FAD (1:1) coamorphous solid induced enhanced invasion of cells from spheroid models. Thus, we propose that CUR-HXQ (1:1) cocrystal possess an effective anti-cancer activity whereas CUR-FAD (1:1) coamorphous solid cannot serve as an ideal candidate for combinatorial drug therapy in the treatment of cancer.

Thus, this work illustrates that the simplicity and geometric compatibility of the coformer molecules to fit into a drug's crystal lattice, strength of the intermolecular interactions between a drug and a coformer, the solubility and therapeutic efficacy of the coformers were found to be the key parameters that determines the successful design of a new pharmaceutical entity with improved dissolution and bioavailability characteristics by cocrystallization.