BESPOKE POLYMERS FOR INHIBITING DRUG CRYSTALLISATION IN AMORPHOUS SOLID DISPERSIONS

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Background: Drug discovery faces a significant hurdle with 70% of emerging drug candidates exhibiting poor aqueous solubility, with many drug compounds falling under Biopharmaceutical Classification System (BCS) Class II/IV. Amorphous solid dispersions (ASDs) have the potential to address this issue by dispersing active pharmaceutical ingredient (API) molecules in an amorphous phase, enhancing dissolution via increased surface area and efficient interactions with the chosen polymer, ultimately, resulting in no lattice energy input required for API molecules to convert from solid to solution. However, there is currently a lack of sufficient knowledge regarding polymer structural activity relationships, hydrophobicity/hydrophilicity effects, and drug-polymer molecular interactions, such as hydrogen bonding. To date, approved ASDs often use cellulose-based polymers, in particular, hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), despite their original designs lacking specificity for ASD formulation. Additionally, current API/polymer screening requires large quantities of API and solvent, resulting in a costly process. Therefore, by deigning bespoke polymers with structurally diverse chemistry, and utilising miniaturised, automated 2D screening of bespoke polymers for ASDs across a 0-100% drug loading (DL) range in 1% increments, this allows for specific polymer excipient design and elucidation of optimised interactions between API and polymer, using microgram quantities of API and polymer.

Methods: Drugs and polymers (both off-the-shelf and bespoke) are printed on silanised glass slides using a Sciflexarray S5, Scienion printer, creating ASDs with 1% DL increments (0-100%). Imaging using the Nikon Eclipse Ni-E microscope utilises both brightfield and polarised light to examine the microarray of each polymer and API combination phase contrast allows the assessment of the opacity and structure of formulations. Cross polarised light allows crystallisation to be visually determined via assessing the DL % in which the ASD converts from an amorphous phase to crystalline, as shown by the development of birefringence, subsequently forming API crystals. Structurally diverse acrylate and acrylamide polymers are synthesised by using RAFT polymerization, allowing control of the molecular weight and narrow polydispersity index, to produce over 40 polymers and 20,000 novel formulation systems.

Results: Proton NMR determines chain length via calculating monomer to polymer conversion. GPC data shown indicates the polydispersity index, whereby polymers with values in the range of 1.0-1.3 are considered to have a good polydispersity index. Results will indicate the potential of bespoke polymers to inhibit crystallisation at higher DL % compared to ‘off-the-shelf’ polymers. Molecular interactions will be modelled to understand key intermolecular forces involved to improve polymer optimisation. Polymers are ranked after stability on the DL% in which crystallisation occurs.

Conclusions: Over 5,000 novel formulations have been generated from both acrylate and acrylamide polymers combined so far with 5 BCS class II/IV drugs. The results from of screening will inform on potential co-polymer combinations.