Crystallization of Active Pharmaceutical Ingredients with Additives and Surfaces
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Many pharmaceutical drugs exist as crystals. A given drug can often crystallize into multiple different forms. The different internal crystal forms of a given crystalline material are called polymorphs, and each polymorph can have different properties.[1] An example of this for pharmaceuticals is that solubility changes between polymorphs, affecting the ability to be absorbed in the human body. Thus, it is necessary for drug developers to control which crystal polymorph they produce for optimal drug performance. Morphology, the outer shape of the crystal, is also important. Crystallization steps now represent a significant portion of the manufacturing process for many drugs.[2] We picked two specific molecules, aspirin and flufenamic acid, as case studies of controlled pharmaceutical crystal growth methods that could possibly be later applied more generally to pharmaceutical molecules.

For both aspirin and flufenamic acid, we grew our crystals from solution. We purchased these molecules in a crystallized form, then dissolved them in a solvent to create a crystal growth solution and then recrystallize them under our own control. We used the technique of spin-coating crystallization on both of our pharmaceutical molecules, in which the crystal growth solution is deposited onto a surface and spun very fast to create a thin, circular film of crystals as the solvent evaporates. The surfaces we used were clean glass slides and self-assembled monolayers (SAMs). SAMs are formed by attaching functional group molecules to a substrate in a single layer, and they can be fine-tuned to change the outcome of crystal growth.[2] We then analyzed the crystalline thin films grown on our surfaces using scanning electron microscopy (SEM). SEM allows us to see detailed images of the outer morphology of the crystals on a very small scale. For flufenamic acid, we did one more growth by slow evaporation of the solvent while the crystal growth solution sits in an open vial. We added an inorganic salt molecule to the crystal growth solution to induce changes in the crystal polymorph,[3] and analyzed the final crystal structure with X-Ray Diffraction (XRD). XRD allows us to see the internal structure of the crystals, or which polymorph we have created.

SEM imaging of aspirin and flufenamic acid thin films revealed that some trials yielded promising morphology, but some trials did not form a thin film like we wanted and instead formed larger lumps of crystals. We determined that in the future, we will need to tweak the procedure for deposition of our crystal growth solution on our glass slides or SAMs during spin coating crystallization. XRD diffraction patterns of our flufenamic acid evaporation growths revealed promising peaks, showing that we indeed obtained crystalline (not amorphous) flufenamic acid. However, our diffraction patterns did not match with the literature as we expected, so further investigation is necessary to determine which polymorph of flufenamic acid we formed.

Faculty Mentor: Amnon Ortoll-Bloch
Funded by the Peter J. Grua and Mary G. O'Connell Summer Research Award

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(3) Byrn, S. et al; Crystal Growth & Design 2008, DOI: 10.1021/cg7008607