Crystallization and Polymorphs: Impact on Performance of Malaria and HIV drugs

Crystal Brickhouse, Adrian Williams, and Dr. Joseph Fortunak
Background Information

- Bioavailability measures the quantity of a drug in systemic circulation vs time (see Fig. 1).
- Drugs must dissolve and be absorbed (mainly in the stomach) to be orally bioavailable.
- Every drug has a unique window of absorption (WOA) which represents the time over which its best absorbed (see Fig. 2).
- Relative bioavailability of drugs change dramatically if their dissolution profile is altered because it will affect absorption within the WOA.
Stages of a medicine's life in the body

- **Absorption**: Medicines can enter the body in many different ways, and they are absorbed when they travel from the site of administration into the body's circulation.
- **Distribution**: Most often, the bloodstream carries medicines throughout the body.
- **Metabolism**: The breaking down of a drug molecule usually involves two steps that take place mostly in the body's chemical processing plant, the liver.
- **Excretion**: Once liver enzymes are finished working on a medicine, the now-inactive drug undergoes the final stage of its time in the body, excretion, as it exits via the urine or feces.
Purpose of Research Project

A solid form of a drug can have very different solubility and dissolution profiles, depending upon the crystalline form it is in. The more stable a crystalline form of a drug, the less soluble it is and this decrease in solubility can affect bioavailability.

Most critical malaria drugs have not been studied to characterize their crystalline polymorphs, solubility and intrinsic dissolution and this is the subject of our work.
Drugs Used

- Amodiaquine
- Artesunate
- Lumefantrine
- Dihydroartemisinin
- Artemether
- Tenofovir Disoproxil Fumarate
Experimental Method

We identified potentially useful solvents

Solutions were prepared by dissolving these drugs and allowing them to crystallize either rapidly (under kinetic control) or slowly (under thermodynamic control)

Some drugs provided more than one crystalline form, displaying differences in physical and spectroscopic behavior

Results are being analyzed through single-crystal X-ray analysis and X-ray powder diffraction, melting point, Infared (IR) and proton (1H) NMR analysis
Results

- Tenofovir Disoproxil Fumarate (TDF) is a drug prepared in a salt form (containing a counterion)
  - Molecular weight: 635.52 g/mol
  - M.p. of a fumaric acid: 287 °C

- This drug recrystallized from 2-propanol as a different salt form (hemi-fumarate rather than a stoichiometric fumaric acid salt) than TDF itself
  - M.p. of a hemifumarate: 100 °C
Results (cont.)

NMR ANALYSIS

Hemifumerate vs Fumarate

The peak on the hemifumarate is half the value of the fumarate

This indicates that the hemifumarate gives a 1:2 ratio for the fumaric acid to tenofovir while the fumarate gives a 1:1 ratio
Results, cont.

Crystal x-rays and polymorphs-still awaiting results
Discussion/Conclusions

By performing this research, hopefully I have created a more bioavailable form of some if not all of these drugs.

Through the obtained results, I will assure that the procedures used by malaria drug manufacturers always supply the same crystalline form.

Ultimately, my research will be transferred to manufacturers of malaria drugs in India and China through the Clinton Health Care Access Initiative.
References


http://www.saladax.com/assets/images/pcm_pharm_fig1.gif


Dr. Fortunak
Acknowledgments

- Amgen Scholars Program
- Dr. Fortunak and Howard University
- Graduate Students