SYDDANSK UNIVERSITET
UNIVERSITY OF SOUTHERN DENMARK

Functional materials and nanotechnology

Application-oriented Crystallization of Pharmaceutical Products

Study of the Chemical and Physical Mechanisms behind drug-polymer interaction as well as co-crystallization.

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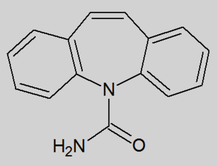
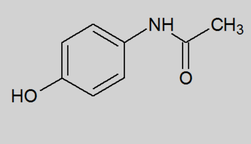
The control of crystal structure for API's showing polymorphism, as well as discovering new polymorphs have become an important part of the drug development. The methods have so far consisted of using different solvents, changing temperature rates or other parameters that have a large impact on production. Lately though, an increased interest in using polymers have emerged. Research has so far been mostly aimed at proving that the idea works and that good results can be obtained, however the interaction between API and polymer is still not understood and thus, experiments tend to adopt a shotgun approach, testing hundreds of polymers for each API.

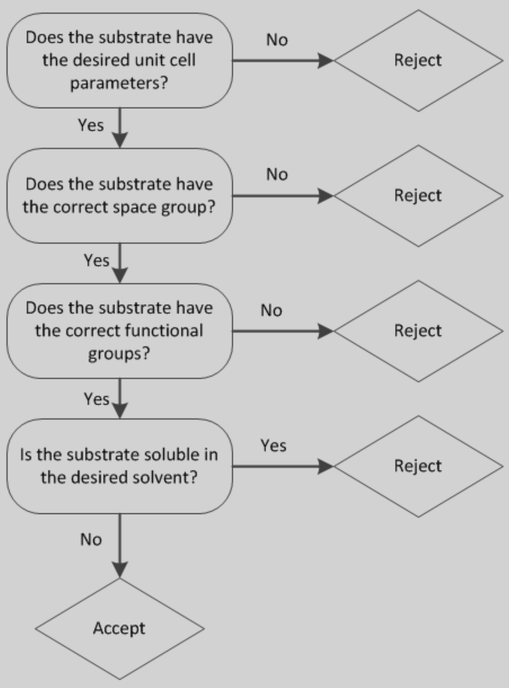


Carbamazepine



Acetaminophen

Selection method of polymers



Effects of crosslinked polymers on acetaminophen

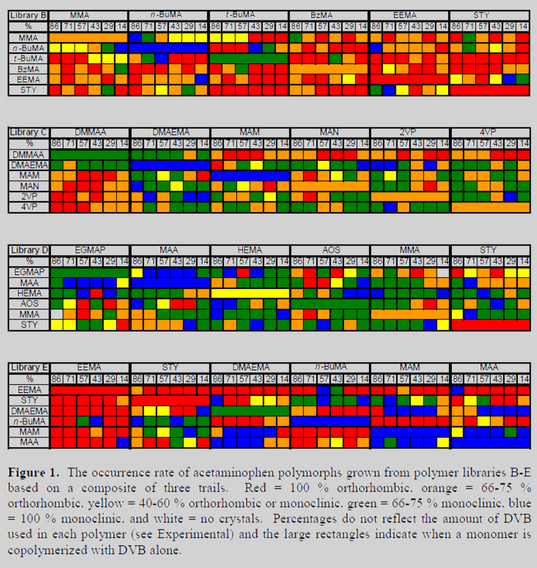


Figure 1. The occurrence rate of acetaminophen polymorphs grown from polymer libraries B-E based on a composite of three trails. Red = 100 % orthorhombic, orange = 66-75 % orthorhombic, yellow = 40-60 % orthorhombic or monoclinic, green = 66-75 % monoclinic, blue = 100 % monoclinic, and white = no crystals. Percentages do not reflect the amount of DVB used in each polymer (see Experimental) and the large rectangles indicate when a monomer is copolymerized with DVB alone.

X-ray powder

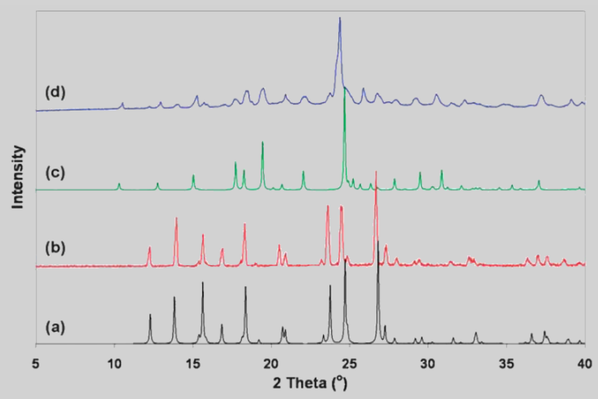


Fig. 3 X-ray powder diffraction data. a) calculated Form I AAP, b) AAP crystallized from pure ethanol, c) calculated Form II AAP and d) AAP crystallized in the presence of 4-APAA.

Goal of the Ph.d.

The main objectives of the project is to develop a better understanding of the mechanisms behind drug-polymer interaction and hopefully improve methods for selecting polymers for specific results. The mechanisms and effects of co-crystals will also be touched upon and compared with polymers to see if similar effects might be at work.

Since there have yet to be established a standard for most of the phenomena investigated, selection and development of measuring techniques will also be part of the project.

Examples of polymorphs from polymers

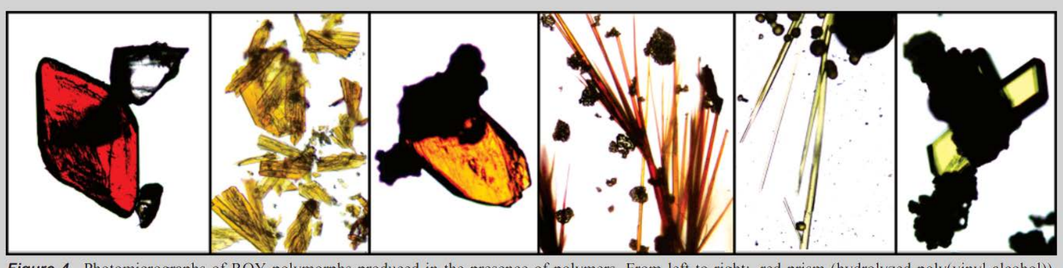
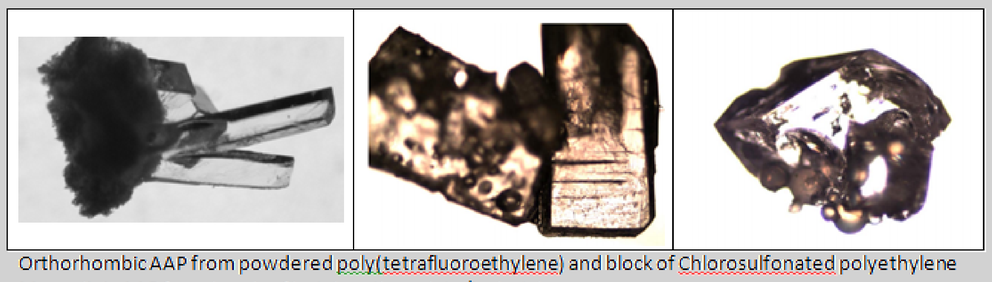


Figure 4. Photomicrographs of ROY polymorphs produced in the presence of polymers. From left to right: red prism (hydrolyzed poly(vinyl alcohol)), orange-red plates (acetoxystyrene/hydroxyethyl methacrylate/divinylbenzene terpolymer, not shown), orange plate (vinyl chloride/vinyl acetate/hydroxypropyl acrylate terpolymer), orange needles (ethylene/propylene copolymer), yellow needles (styrene/butyl methacrylate copolymer), and yellow prism (vinyl chloride/vinyl acetate copolymer).



Orthorhombic AAP from powdered poly(tetrafluoroethylene) and block of Chlorosulfonated polyethylene
Monoclinic AAP from beads of butyl methacrylate/isobutyl

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Lang, M., Grzesiak, A.L., Matzger, A.J., 2002. The Use of Polymer Heteronuclei for Crystalline Polymorph Selection. J. Am. Chem. Soc. 124, 14834–14835.
Llinàs, A., Goodman, J.M., 2008. Polymorph control: past, present and future. Drug Discov. Today 13, 198–210.
López-Mejías, V., Knight, J.L., Brooks, C.L., Matzger, A.J., 2011. On the Mechanism of Crystalline Polymorph Selection by Polymer Heteronuclei. Langmuir 27, 7575–7579.
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