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Solid-state deracemisation by Viedma ripening

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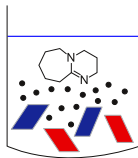
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1. What is Viedma ripening?

Viedma ripening, or attrition-enhanced deracemisation, is a process to obtain enantiomerically pure crystals.

Process:[1,2]
- Start with crystals of both enantiomers (conglomerates)
- Add racemising agent (or use achiral molecule, eg. $NaClO_3$)
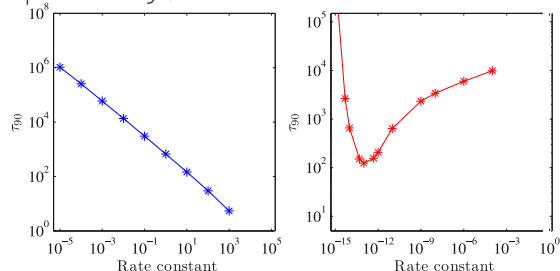- Thermal or mechanical treatment

Mechanism:[1,3-6]
- Racemisation in solution (enantiomers interconvert)
- Attrition creates small crystals
- Dissolution of small crystals
- Growth of large crystals
- Agglomeration removes small crystals by creating large particles

2. PBE Model[6]

Growth & dissolution
- Solubility is size-dependent (Gibbs-Thomson effect)
- Small crystals will dissolve, large crystals will grow
- Only mechanism allowing transport between phases
- Modeled by use of size-dependent growth rate

$$G_i = k_g \left(\frac{c_i}{c_\infty} - 1 - \frac{\alpha}{x} \right)$$
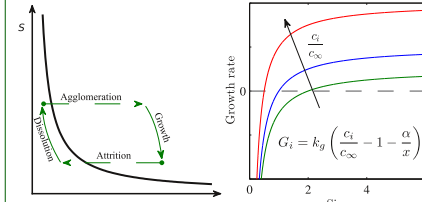
Agglomeration
- Rate of agglomeration is second-order in particle concentration
- Enantioselective agglomeration only
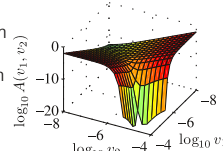
Breakage
- Rate of breakage is first-order in particle concentration
- Breakage by attrition yields two particles: one small and one large

- One PBE for each population of crystals
- Coupling with mass balances for the enantiomers in solution

$$\frac{\partial n_i}{\partial t} + \frac{\partial (G_i n_i)}{\partial x} = B(x) - D(x) \quad i = L, D$$

$$\frac{dc_L}{dt} = -k_v \rho \frac{d\mu_{L,3}}{dt} + k_r (c_D - c_L)$$

$$\frac{dc_D}{dt} = -k_v \rho \frac{d\mu_{D,3}}{dt} + k_r (c_L - c_D)$$

Racemisation
- Affects molecules in solution
- First-order reaction, equilibrium at racemic composition

3. Breakage vs. agglomeration

Comparison of effect of rate of agglomeration vs. rate of breakage. Plot shows time required to reach 90% enantiomeric excess.
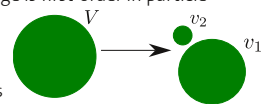

The breakage rate has a very strong effect on the rate of the process, as observed in experiments[1,7-9]. However, the process time is finite even at zero breakage rate. Towards very low agglomeration rates, the process time tends towards infinity.

No breakage -> slow deracemisation, but successful
No agglomeration -> no deracemisation

4. Influence of initial conditions[10]

The direction of evolution and the deracemisation time are strongly dependent on the initial conditions. The left figure shows how different the outcome of 100 simulations with slightly varying initial conditions can be.

Randomly varying:
- *ee*
- mean size
- width around point of symmetry
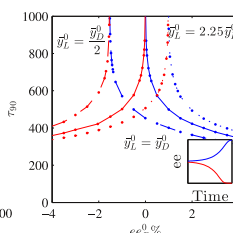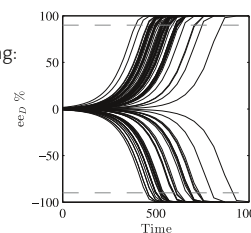
The sensitivity of the deracemisation time to the initial conditions is very high near the point of symmetry (the peak of the curve), even for only one variable being varied. Thus, small variations can lead to large differences in process time.

Direction of evolution depends on biasing present in initial conditions. This is affected by the mass, particle size, and size variation.

## 5. Experiments: temperature cycling and grinding

- Temperature cycles shown to work previously[11]
- **NMPA in methanol with DBU**, initial solid phase excess of 10%
- Varying cycle times
- Heating/cooling times as fraction of total cycle time is constant
- Initial excess of (R) in solid phase: 10%
- Initial solid created by crystallisation from solution with excess: ensures homogenous distribution between (R) and (S)
- 3-4 identical experiments run in parallel
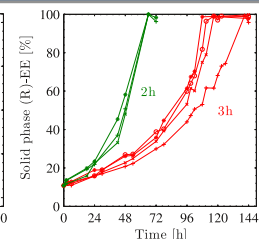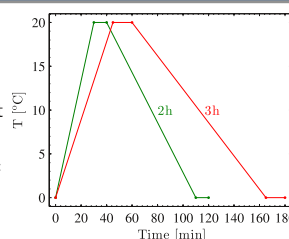
- Shorter cycle time leads to faster deracemisation
- Results reproducible between identical experiments
- Experiments show that there is substantial room for optimisation
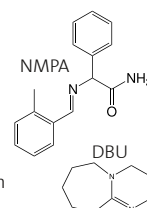
- **High Pressure Homogenisation (HPH)[12]:**
- Reactor vessel containing suspension of NMPA and DBU
- Circulation of suspension via high-pressure pump through homogeniser, recycled to vessel
- Pressure release across homogeniser leads to comminution of particles through high shear
- Temperature of suspension increases when passed over homogeniser
- Process commonly applied in biotech and food processing

Additional co-authors for HPH work: MP Fernández-Ronco, R Senn, J Kluge
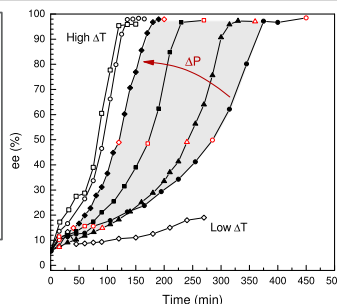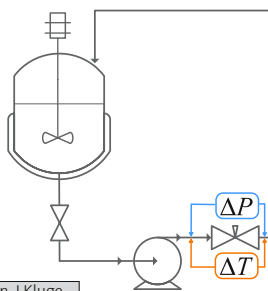
- Closed symbols: higher pressure drops lead to larger temperature difference and to faster deracemisation.
- Open symbols: homogeniser temperature changed by external temperature control. Shows large influence of temperature difference on process.
- Process advantage: good temperature control, no separation of grinding media at end, fast deracemisation: hours instead of days.

6. Conclusions

- The presented population balance model explains and reproduces all experimental observations reported in literature.

- Breakage is important for the rate of deracemisation, but deracemisation takes place even without breakage. However, deracemisation does not take place without agglomeration.

- Imbalance in initial conditions of the two populations (mass, mean size, width) is amplified. Process time is very sensitive to exact initial conditions, needs to be taken into account in application.

- The model presented in this work fills crucial gaps in understanding Viedma ripening and contributes to making its exploitation possible.

- Grinding can be replaced by temperature oscillations, with similar behaviour.

- HPH: Existing technology applied to Viedma ripening. Combination of temperature oscillations with grinding leads to fast processing, reducing process times from days to hours.

References

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