On-line Monitoring of the Spherical Crystallization of Salicylic Acid

Omar S. Hasan¹
Helen M. Buettner¹
San Kiang²

¹ Department of Chemical and Biochemical Engineering
Rutgers, The State University of New Jersey, Piscataway, NJ

² Bristol-Myers Squibb Co., New Brunswick, NJ

Lasentec FBRM Users Conference,
Orlando, FL
March 2000
Introduction

• Almost all bulk chemicals produced by the pharmaceuticals industry are crystalline.

• Dosage form production is often hindered due to the poor processability of the bulk chemicals.
  – Poor powder flow properties
  – Low compactability

  ➢ Result: product loss, environmental hazards, increased cost

• Spherical crystallization has been shown to produce bulk chemicals with improved processability (Kawashima, 1994).

• However, the effects of process parameters on the spherical crystallization process are not well understood.
Spherical crystallization background

- Spherical crystallization: crystallization and agglomeration of a material occur simultaneously in the same liquid system.

- Binary or ternary mixed solvent system is chosen as the crystallization solvent.

- **Mechanisms** (Kawashima, 1994)
  1. Spherical agglomeration (SA)
  2. Emulsion solvent diffusion (ESD)
Spherical crystallization mechanism

- Precipitation of drug crystals induced through addition of “good solvent” solution of drug to “poor solvent”
- “Bridging liquid” is present which preferentially wets drug particles and collects them to form agglomerates
- Under agitation, agglomerates are spheronized, forming spherical crystal agglomerates (SCAs)
Effect of bridging liquid: previous work

- **Qualitative (imaging)**
  - Larger agglomerates observed with increased bridging liquid concentration (Kawashima et al., 1982; ibid., 1984).

- **Quantitative (sieve analysis)**
  - Average diameter increases with bridging liquid concentration (Kawashima et al., 1983; Ueda et al., 1991).

- **Problems:**
  - Sieving technique can be destructive to spherical crystals and can lead to inaccurate measurement of PSD
  - Difficult to measure PSD as a function of time

GOAL: Development of a reliable, non-destructive and continuous method for size measurement of spherical crystals
Selection of bridging liquid

• Agglomeration activity of bridging liquid is believed to be determined by its physical properties, such as surface tension or solubility.

• Relationship between these properties and resulting agglomerate size is unclear (Kawashima et al., 1984).

  » GOAL: develop better understanding of relationship between physical properties of bridging liquid and agglomeration activity

• Rational design of spherical crystallization systems that are acceptable for pharmaceutical processing (non-toxic, environmentally benign, inexpensive, etc.)
On-line particle size analysis

- Well-characterized methods of measuring particle size distribution (PSD):
  - sieve analysis
  - microscopy - image analysis
  - off-line particle size analysis

- On-line particle size analysis, a technique based on light scattering, is an increasingly common means of measuring PSD (Hobbel et al., 1991; Dost et al., 1996).

- On-line particle size analysis has several advantages
  - non-intrusive
  - continuous and instantaneous monitoring of process
On-line particle size analysis

- **Wide range of chemical processing applications:**
  - Aerosols (Jerkovic and Fissan, 1993), Emulsions (Sparks and Dobbs, 1993), Liquid jets (Schuchmann and Schubert, 1993)

- **Crystallization applications:**
  - Sucrose (Brown and Alexander, 1990), Ammonium sulfate (Jager et al., 1990), Copper sulfate (Karakaya et al., 1990)

- **Concerns:**
  - In many cases, equipment is constructed for the specific application and results are difficult to reproduce.
  - Dilution techniques are often necessary which can influence the measured PSD.
On-line particle size analysis: FBRM applications

- **Characterization of FBRM**
  - Influence of FBRM operating conditions on monitoring of suspensions of glass beads (Monnier et al., 1996)
  - Influence of particle geometry on CLD measurements (Tadayyon and Rohani, 1998; Simmons et al., 1999)

- **Previous reports of FBRM**
  - Emulsions (Mason et al., 1995)
  - Crystallizations (Farrell and Tsai, 1995)

- **Advantages:**
  - standardized equipment
  - no dilution techniques necessary
Experimental setup

- **Mettler Toledo LabMax automated lab reactor**
  - Glass reaction vessel of diameter $T = 10$ cm
  - Jacket temperature controlled by LabMax to maintain contents at 5°C.
  - Agitation at 300 RPM by glass four-blade pitched-blade impeller with a diameter $D = 5$ cm.
Spherical crystallization methods

Model system
(Kawashima, 1982; Kawashima et al., 1984)

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Material</th>
<th>Percent (v/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>drug</td>
<td>salicylic acid</td>
<td>n/a</td>
</tr>
<tr>
<td>“good” solvent</td>
<td>ethanol</td>
<td>16.3 – 16.7</td>
</tr>
<tr>
<td>“poor” solvent</td>
<td>water</td>
<td>81.3 – 83.3</td>
</tr>
<tr>
<td>bridging liquid</td>
<td>chloroform</td>
<td>0.0 – 2.4</td>
</tr>
</tbody>
</table>

Methodology
- Poor solvent and bridging liquid added to tank and cooled to 5 C.
- Drug dissolved in good solvent and maintained at 25 C.
- Suspension agitated to allow completion of process.
- Samples plated on microscope slides for analysis.

→ Other bridging liquids: ethyl acetate, hexane, toluene
Lasentec D600 Monitoring System

FBRM probe dimensions

Probes located within 1 cm of impeller tip to ensure good flow across probe window

Probe located within 1 cm of impeller tip to ensure good flow across probe window
Experimental apparatus

Air and fiber optic cables

Impeller

Probe tip
Measurement and data acquisition setup

- **Measurement timing**
  - Goal: statistically representative sampling of the system
  - Measurement duration must be faster than characteristic time scale of process
  - Measurement time: 10 sec.

- **Data acquisition**
  - Goal: high sensitivity to process changes
  - Number of channels, channel configuration: 1 - 1000 micron, log scale
  - Time between data acquisitions: 30 sec.

⇒ Some *a priori* knowledge of process is necessary before setting measurement parameters
Validation of FBRM measurements

- Validation of FBRM measurements is necessary
  - relating CLD to PSDs obtained by other methods
  - better interpretation of CLD data

- An accurate measurement of the PSD can be obtained by optical microscopy combined with image analysis techniques (Pons and Vivier, 1991; Davidson and Butler, 1992; Hasan et al., 2000).

- Microscopy and image analysis techniques have been developed at Rutgers and were used to obtain the PSD of crystal samples taken from experimental runs.

- The FBRM technique was validated by comparing results to that obtained using optical microscopy.
Microscopy and image analysis methods

- Microscope
  - 2X magnification
  - Programmable stage

- PC

- PSD

- 2.5 mm
- 3.4 mm
- 17.5 mm
- 23.8 mm
Validation of FBRM measurements

**Chloroform system, 2.4 % v/v**

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>FBRM</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>86.5 µm</td>
<td>115.9 µm</td>
</tr>
<tr>
<td>Length-weight mean</td>
<td>315.1 µm</td>
<td>278.4 µm</td>
</tr>
</tbody>
</table>

**Percent difference**

25.4 %

13.0 %

**Toluene system, 1.3 % v/v**

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>FBRM</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>87.0 µm</td>
<td>119.3 µm</td>
</tr>
<tr>
<td>Length-weight mean</td>
<td>171.0 µm</td>
<td>288.8 µm</td>
</tr>
</tbody>
</table>

**Percent difference**

27.1 %

40.8 %
Results: standard crystallization of salicylic acid

- Mean chord length of salicylic acid crystals at steady-state is about 15 μm.
- Some natural agglomeration is observed (30% drop in particle count).
- Small standard deviation between runs demonstrates that experimental results are highly reproducible.
Results: Effect of chloroform concentration

Increasing chloroform concentration

0.82 % (v/v)  1.6 % (v/v)  2.4 % (v/v)
Results: chloroform system

- Mean chord length at steady-state increases with increasing chloroform concentration.

- Number of particles decreases with increasing chloroform concentration.

- For low concentrations of chloroform, steady-state conditions reached very quickly (within five minutes).
Initial CLD is log-normal at both chloroform concentrations.

At lower concentration of chloroform, CLD is fixed after 2 minutes.

At higher concentration of chloroform, CLD is fixed after 30 minutes.
Results: toluene system

- Trends in both mean chord length and particle count with toluene concentration are similar to that observed in the chloroform system.

- Amount of toluene necessary to form SCAs is less than chloroform needed.

- Steady state conditions reached more slowly than in chloroform system, (within 30 minutes).
• At both concentrations of toluene, CLD is fixed after about thirty minutes.

• Larger SCAs produced with higher amount of toluene.
Results: ethyl acetate system

- Similar trends in mean chord length and particle count observed as in previous systems.
- SCAs are very small compared to those produced in previous systems.
- Results are fairly insensitive to ethyl acetate concentration, even at 6 % v/v.
Results: ethyl acetate system

- With both concentrations of ethyl acetate, the CLD is constant after about 5 minutes.
- Much less agglomeration is observed in this system compared to the previous systems.
• Particle count decreases with increasing amount of hexane in the system.

• At the highest level of hexane, the mean chord length dropped after 1 hour: particle breakup or instrument limitation?

• Steady-state conditions reached very slowly, requiring up to 2 hours.
Results: hexane system

- With low level of hexane, the CLD continues to shift towards larger particles even up to 2 hours.

- Very large SCAs produced were produced with the higher level of hexane, leading to particle breakup and undercounting of largest particles.
Conclusions

• Lasentec system can be used to monitor formation of spherical crystal agglomerates (SCAs) of salicylic acid.

• CLD data obtained using the Lasentec was validated against experimental measurement of the PSD from optical microscopy and image analysis.

• For four systems, changes in the kinetics of SCA formation were observed as a function of bridging liquid concentration.

• The agglomeration activity of each system was dependent on the material used as the bridging liquid.
Acknowledgements

• Bristol-Myers Squibb:
  – Mark Lindrud
  – Dr. Chenkou Wei

• Rutgers University:
  – Nga Tran
  – Jean Condon

• Funding Sources:
  – National Science Foundation
  – Rutgers University Pharmaceutical Engineering Training Program
  – Rutgers/NJIT Particle Processing Research Center