



# RAPID QUANTITATIVE PHYSICAL STABILITY DEVELOPMENT FOR PHARMACEUTICAL SUSPENSIONS

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## ABSTRACT

**Purpose:** Parenteral suspension formulation development requires rapid screening of potential wetting and suspending agents to understand and predict possible agglomeration and settling of the active pharmaceutical ingredient. We developed a "stop-mixing" technique utilizing the Lasentec FBRM (Focused Beam Reflectance Measurement) to monitor and analyze micro-suspensions in real-time to assist in the rapid development of a parenteral suspension product.

**Method:** Several excipients including a wetting agent (tween 80), suspending agent (block copolymer), and salt (sodium chloride) were chosen for their properties in suspension development. Various levels of each were evaluated. After achieving a well dispersed steady-state suspension, the agglomeration and settling behavior of the suspension was monitored using the Lasentec FBRM to provide real time analysis of the suspension.

**Results:** Initial assessment of a suspension containing 1% Tween 80, 1% block copolymer in 10 mg/ml API was evaluated for settling rates. Initially, 1-5 micron particles decreased in count rate (chords/sec) with a corresponding increase in larger particles (>29 microns). Based on the particle mass balance, smaller particles were agglomerating to form flocs. Increases in stabilizer or salt concentration resulted in a significant delay in the rate of formation of larger flocs and increased the time flocs were suspended. A similar degree of flocculation and settling rates were seen with 1% NaCl or 3% block copolymer. Suspension stabilization through a polymeric steric stabilizer has a similar effect as a controlled flocculation approach utilizing NaCl.

**Conclusions:** Data gathered utilizing the Lasentec FBRM enabled rapid development of a parenteral suspension. We concluded that addition of higher levels of block copolymer lead to stabilization of the particles against agglomeration. Sodium chloride also provided similar stabilization results as the addition of higher block copolymer levels to the suspension performance. This knowledge allowed us to efficiently select the appropriate formulation to maximize the formulation performance.

## PHARMACEUTICAL SUSPENSION DEVELOPMENT

Physically stable dispersions of a drug in a suitable suspension vehicle are important to create a drug product with:

- Consistent and reproducible dosage
- Predictable shelf life
- Batch to batch consistency

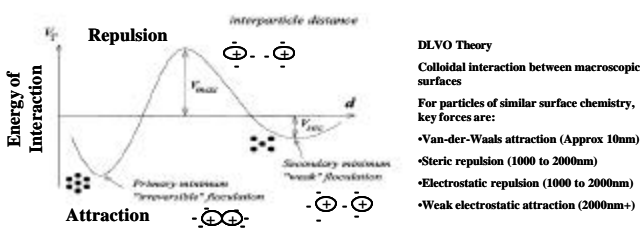
Rapid suspension development screening (desirable):

- Understand and predict flocculation and settling of the active pharmaceutical ingredient using potential wetting and suspending agents.

Development of a "stop-mixing" technique (desirable):

- Monitor and analyze micro-suspensions in real-time utilizing the Lasentec FBRM (Focused Beam Reflectance Measurement).

## FLOCCULATION IMPORTANCE IN PHYSICALLY STABLE SUSPENSIONS



Deflocculated	Flocculated
Particles exist in as separate entities.	Particles form loose aggregates.
Rate of sedimentation is slow. Particles settle separately, particle size is minimal.	Rate of sedimentation is high Particles settle as a floc (collection of particles)
The sediment is formed slowly. The sediment is very closely packed	The sediment is formed rapidly. Sediment is loosely packed
<ul style="list-style-type: none"> <li>• Increasing settling weight from upper layers of sedimenting material.</li> <li>• Repulsive forces between particles are overcome and a hard cake is formed</li> <li>• The sediment is difficult, if not impossible, to redispense.</li> </ul>	<ul style="list-style-type: none"> <li>• Possesses a scaffold-like structure.</li> <li>• Particles do not bond tightly to each other and a hard, dense cake does not form.</li> <li>• The sediment is easy to redispense, so as to reform the original suspension.</li> </ul>

## METHOD SUMMARY

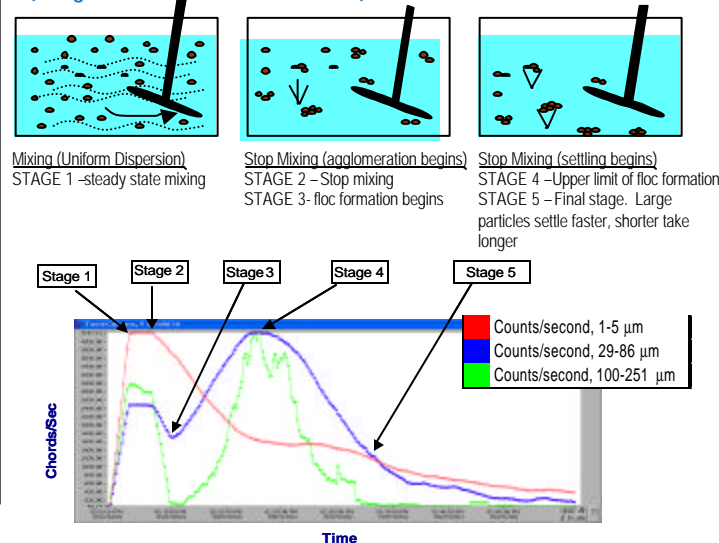
- **Objective:**
  - Control settling and understand flocculation of a pharmaceutical suspension using a wetting agent, stabilizer, and/or salt.
- **Materials:**
  - Suspended API, "Compound P" low MW pharmaceutical API (10mg/ml)
  - Tween 80, wetting agent
  - Block copolymer (BCP), stabilizer
  - NaCl, control flocculation
- **Experimental studies**
  - Mechanistic study of settling in API suspension
  - Reproducibility of identical experiments (for multiple runs/identical trends, data not shown)
  - Settling study
    - Effect of varying stabilizer (BCP) amount
    - Effect of varying flocculant controller (NaCl) amount
- **Analytical Tool:**
  - Monitor suspension settling/ flocculation using Lasentec FBRM, a real-time and in-line particle size analyzer.

## LASENTEC® FBRM (SERIES S400Q)

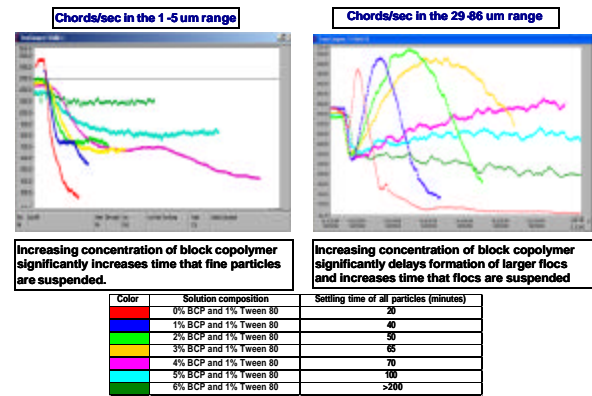
**How does Lasentec® FBRM system work?**

- Quantify, in real time, the rate and degree of change to particle dimension, particle population, and particle shape.
- System does not assume spherical particles. Measures particle sizes from 0.5 μm to 2.5 mm and track most processes from 0 to 3 mm.
- Distribution weighting – unweighted (count based focus on fines) and/or cube weighted (focus on coarse material)
- No sampling required for measurement (no dilution, dispersion in a different solvent, sonication).
- Areas of application and interest in liquid formulations: Crystallization/Precipitation, Flocculation, Dispersion, Emulsification, Homogenization, etc.
- Reference: <http://www.lasentec.com>

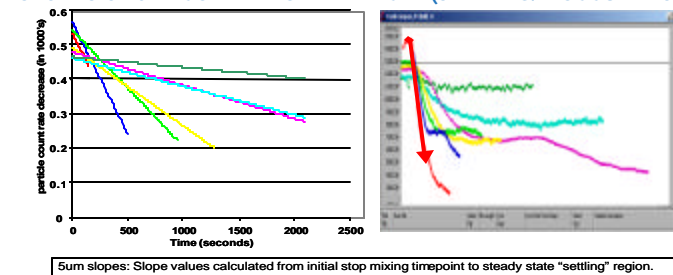
## EVALUATION OF "STOP MIXING" TECHNIQUE (10mg/ml in 1% Tween 80, 1% BCP)



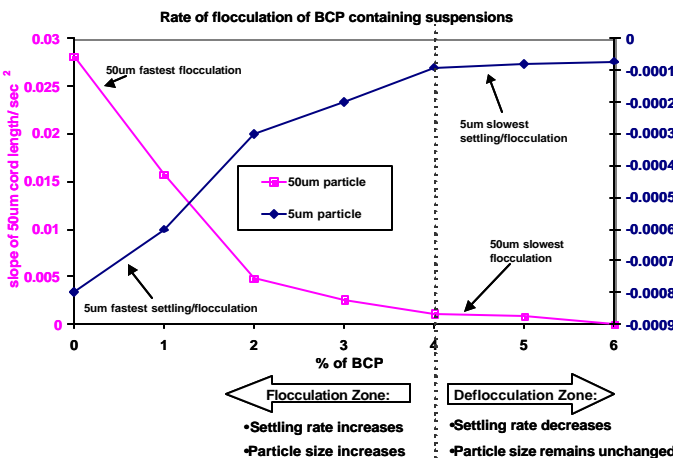
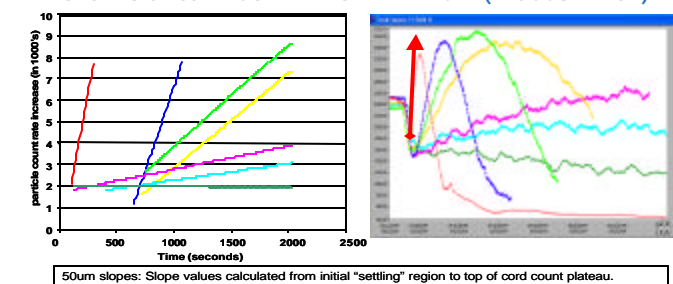
## MONITORING EFFECTS OF 0 – 6% BLOCK COPOLYMER (BCP)



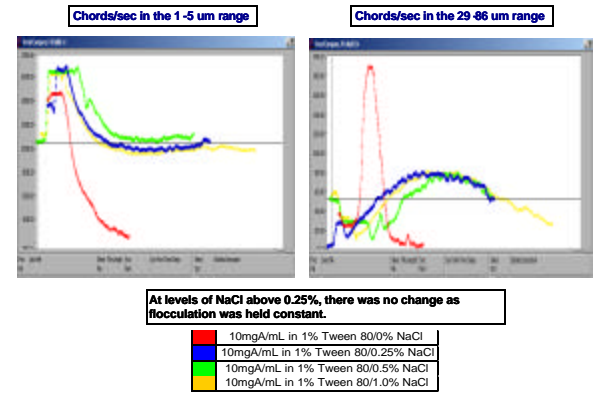
## SLOPES OF 5mm CORD LENGTH PARTICLE (SETTLING/FLOCCULATION)



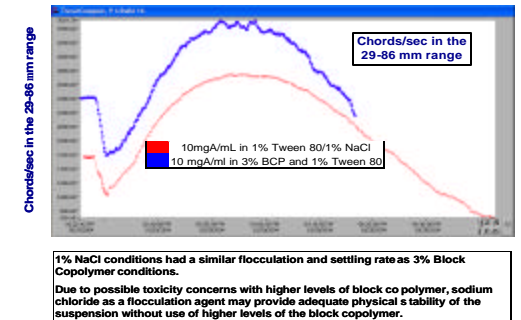
## SLOPES OF 50mm CORD LENGTH PARTICLE (FLOCCULATION)



## MONITORING EFFECTS OF 0 – 1% SODIUM CHLORIDE



## COMPARING 1% NaCl TO 3% BLOCK COPOLYMER



## CONCLUSION

1. Increasing concentration of block copolymer:
  - Inhibits flocculation and thus serves to stabilize the suspension.
  - Data provides support for its use as a steric stabilizer.
2. Addition of sodium chloride to control flocculation:
  - Similar results to higher block copolymer levels
  - Can be used as an alternative due to possible toxicity issues with higher block copolymer levels.
  - Data provides support for the DLVO theory and NaCl as an ionic stabilizer.
3. Lasentec FBRM real time process analytical technology (PAT)
  - Quickly quantify and characterize the dynamic properties of particle distributions in liquid suspension without sampling or sample preparation.
  - Identify the multi-stage settling mechanism for suspension of API including particle settling and particle fines agglomerating to form flocs.

## ACKNOWLEDGEMENTS

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