Electronic Supplementary Material (ESI) for CrystEngComm.

Evaluation of Focused Beam Reflectance Measurement (FBRM) for Monitoring and Predicting Crystal Size of Carbamazepine in Crystallization Processes

A. Literature Review: Impact of Process Variables on FBRM

The measurement from FBRM could be affected by many variables such as mixing, crystal shape, orientation, optical properties, etc.[1-3] Barret and Glennon demonstrated that the total number of counts measured is a function of solid concentration and probe location for dilute agitated suspensions.[4] Recent work showed that there is some proportionality between the chord length and solid concentration in diluted regions, but the chord length decreases at higher solid concentrations after a maximum point (e.g. 1.1%).[3] Hence, the impact of solid concentration on the total number of counts and chord length measurement varies as the solid concentration range changes.

The shape and orientation of particles may also have a significant impact on the chord length measurement. Precise and accurate measurements have been achieved for only spherical particles since the chord length estimation can be related as measurements of bounds of 2D projections of the particle.[5] As the particle deviates from spherical (e.g. plate, needle-like) shape, the measurement can vary significantly with respect to the orientation of the particle. For example, the chord length of needle-shaped particles will depend significantly on the orientation of the particles (the probability of a long needle to be aligned with the detection beam is low). Therefore, the boundary of the detected chord length will vary significantly on the axis in which the cut occurs (i.e. length or width). [6]

Optical properties of the measured system may also affect the chord length measurement. The intensity of the reflected light depends on the contrast between the medium and the particle: the larger the difference between the refractive indices of the particle and the medium is, the stronger the intensity of the reflected light will be. Yu and Erickson demonstrated that the intensity variance impacts the FBRM measurements by monitoring PVC particles in different systems.[3] Also, transparent crystals or facets may result on reflection or refraction of the laser beam;[7] this may lead to a phenomenon called “chord splitting” in which a long scanning path on a surface is detected as multiple short chords.[8-11]

Mathematical methods have been developed considering optical property’s effect on the CLD measurement. For example, a mathematical model of the probe and its optical properties is used to transform particle size distribution to chord length distribution.[10, 11] However, these models are complex and computational expensive. Other alternatives consider the probability of particles of specific morphology to be measured. Simpler models, such as geometric models, involve the assumption of 2D projection of the particles.

B. Assessment of FBRM Using Ideal Glass Beads

Glass spherical beads of 100μm size were acquired from Scientific Industries, InC. The size distribution of glass beads was characterized using laser diffraction (HELOS, Sympatec). The spherical glass beads acquired from Scientific Industries Inc. were characterized using laser diffraction. The average size distribution is shown in Figure B.1. The off-line laser diffraction characterization shows that the mean size is around 136 μm.

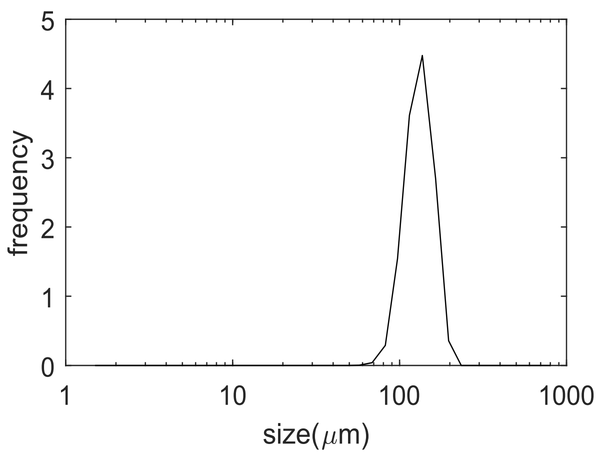


Figure B1. Size distribution of glass beads obtained from off-line laser diffraction.

The precision of the FBRM was studied by monitoring spherical glass bead particles described in supplement B. The intra-day study was performed by monitoring 10g of glass beads in 300 mL of water at 400rpm. The suspension was monitored over a period of 5 min. The system was shut-down and initiated after 15 min. Then, the same suspension was monitored following the same protocol. This was performed a total of three times in one day. The inter-day precision study was done by monitoring 10g of glass beads in 300mL of water at 400rpm over a period of three consecutive days. The system was monitored for 30 min before stopping the FBRM and the agitation. The agitation and the FBRM was initiated the next day, and the same suspension was monitored for 30 min. This procedure was performed for three days to evaluate the variance of the FBRM measurement for the exact system.

The impact of process variables on the FBRM statistics was studied using spherical glass beads. The effect of agitation speed was studied by monitoring 10g of glass beads at 4 agitation speeds (i.e. 200, 300, 400, and 500 rpm). The glass beads were suspended in 300ml of water. The same study was performed for clear water (no solids). The system was monitored for 5 min at each agitation speed before performing a step change (e.g. 200 to 300 pm). This study was performed three times. The impact of solid concentration was studied by monitoring the addition of 1g of glass beads to the system. The glass beads were added in 1g increments, every 4-5min, until 10g was reached. The agitation and the volume were fixed to 300rpm and 300mL for this study. The study was performed three times to consider the variability of the instrument on the measurement.

B.1. Precision study

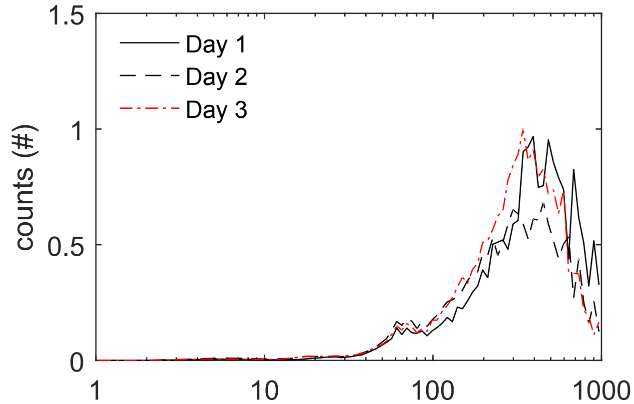
FBRM is commonly used as a qualitative tool to monitor the dynamics of batch crystallization process. Also, it has been used to determine the state of operation in continuous processes.[12-15] As a tool used to monitor the process dynamics it is necessary to study and evaluate the precision of the instrument. The initial study involves evaluating the precision of the instrument with ideal spherical particles. The CSD was estimated off-line and an average mean size of 131μm (i.e. d_{50}) was obtained. The precision studies were performed at constant agitation rate (400rpm) and solid concentration (33 mg/mL). The agitation rate was fixed to 400rpm since it is the maximum possible before observing bubbles for the system considered.

Intra-day precision studies were performed to assess the variability of the instrument statistics within one day at short intervals; measurements were saved for 5 min but the last minute was considered for the calculations (six measurements). The instrument was turned off for a minimum of 15 min before initiating the next set of measurements. A total of three replicates were performed in an hour. The average values for the total counts and square weighted mean chord length (SWMCL) for a macro no weighted distribution is shown in Table B.1. The intra-day study shows that the relative standard deviation (RSD,%) for the SWMCL and total counts its below 3%. The average SWMCL obtained is 136.7μm which is close to the d_{50} estimated with off-line laser diffraction. The average total count is relatively low for the solid concentration considered (33 mg/mL). The low number of particles detected could be attributed to the optical properties of the glass beads.[16] Nonetheless, the RSD shows good repeatability of the instrument at the high solid concentration studied.

Table B.1. Summary of precision study for glass beads at 400rpm and solid concentration of 33 mg/mL

FBRM statistics Macro No Wt.	Intra-day (n=18)			Inter-day (n=18)		
	Average	**Conf. Int. (95%)**	**RSD (%)**	**Average**	**Conf. Int. (95%)**	**RSD (%)**
SWMCL (μm)	136.7	1.47	2.33	153.6	2.46	3.47
Total counts (#/s)	550.5	7.27	2.86	442.4	7.74	3.79

The inter-day precision study was performed for similar conditions as the intra-day study. The system was monitored for 30 min and the last minute (6 measurements) was used for calculations. The RSD within each day evaluated ranged between 0.69-1.85% for SWMCL and 0.07-0.36% for total counts. A total of 18 measurements were considered. The inter-day precision study shows the similar trend as the intra-day; the RSD obtained for the total counts is larger than the SWMCL while very low counts are achieved. As explained before, this could be due to the optical properties of the particles and solvent. Similar optical properties can cause the 'chord splitting' phenomenon that can affect the instrument measurements. Moreover, lower counts and higher SWMCL was obtained for the inter-day study which can indicate some drift of the instrument through days. The RSD obtained for the inter-day study is larger than the intra-day study which can be associated to some drift. For the inter-day precision study, the suspension of glass particles was not disturbed, and the probe was not moved from the location. Hence, the variance observed can be attributed to the instrument measurement for this type of particles. 'Chord splitting' could occur for this type of system since the glass particles are clear; higher variability can be expected over the various studies using glass particles. This can be observed for the average CLD measured for inter-day precision study (refer toFigure B.2.); significant noise can be observed for the average CLD measured each day. Nonetheless, the shape of the CLD is similar every day with the major difference is the counts in various size bins.

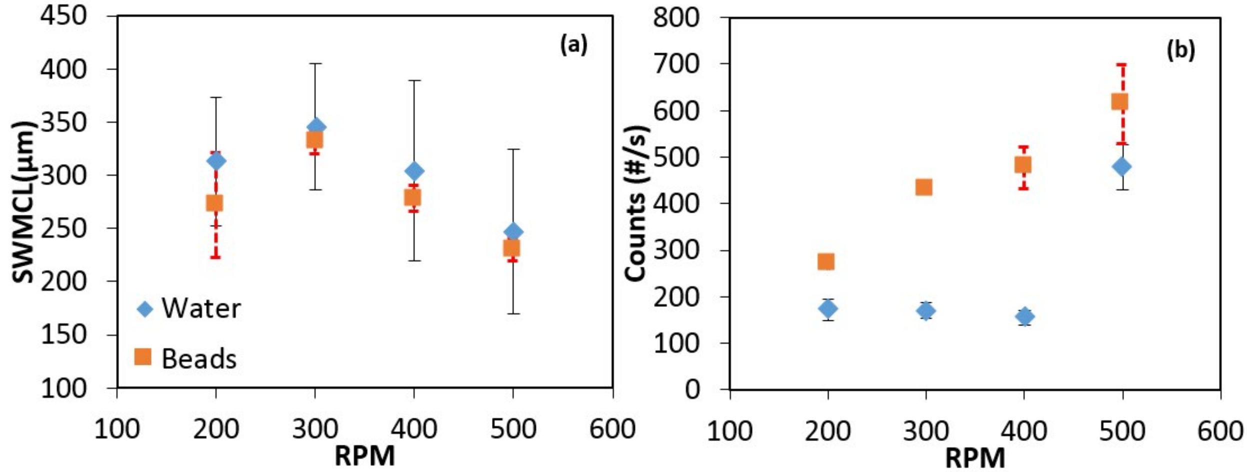


FigureB.2. Average CLD for glass beads suspension monitored for 30 min on three consecutive days.

B.2. Effect of agitation speed and solid mass

The effect of agitation speed on FBRM statistics for ideal spherical particles was evaluated through a series of batch experiments. The suspension of glass beads of specific amount was monitored at the desired agitation speed (e.g. 200, 300, 400, or 500 rpm). The study was performed for clear solvent (i.e. water only) to evaluate differences in the measurements with and without solid. Figure 5 shows the variation of the SWMCL and total counts with respect to changes in agitation speed for solvent (i.e. water only) and suspension (i.e. glass beads and water). The standard deviation for the SWMCL is significantly larger when the water is only monitored compared to when the suspension is monitored. Nonetheless, the average values are in the same order of magnitude; this can be an indication of the issues present whenever the solvent and particle have similar optical properties.

The SWMCL is lower for the suspension compared to the water only for all agitation speeds considered. A difference of 41.0 μm was observed at 200 rpm, while a difference between 13.8, 25.6, and 17.2 μm was obtained for 300, 400, and 500 rpm, respectively. Also, a decreased is observed on the standard deviation of the SWMCL for the suspension between 200 and 300 rpm. This could be a mixing effect in which 200rpm is too low for the suspension to be well-mixed; hence, larger variance on the measurement will be observed for poorly mixed system. A decrease of approximately 50 μm is observed when the agitation speed is increased between 300 to 400 rpm; a decrease of similar magnitude is observed when the agitation is increased from 400 to 500 rpm. The decrease could be related to the probability of more particles being scanned by the laser or double counting the same particle at each rotation scan; this allows for more consistent measurements of the SWMCL since more ideal spherical particles of uniform size distribution are being measured. Hence, the agitation speed (300-500 rpm) is inversely proportional to the SWMCL for this system which is well-mixed with uniform size distribution and spherical shape.



FigureB.3.. Impact of agitation speed (rpm) on (a) SWMCL and (b) total counts for water only (diamond) and beads suspension (square).

The total counts shown in Figure B.3(b) demonstrate significant difference between the magnitudes observed for the water only and beads suspension scenarios. The total counts for the water only scenario are below 300 #/s for 200,300 and 400rpm; this is within the manufacturer recommended counts for clear solvents (i.e. <300 #/s). However, an increase is observed at 500rpm above the recommended threshold of 300 #/s. This can be related to bubbles being generated due to the turbulent mixing. The FBRM can detect bubbles which would affect the measurements.[17, 18] The impact of the turbulent mixing and generation of bubbles on the suspension can be observed for the average total count at 500rpm; a significant increase on the average total counts and standard deviation is observed for the beads suspension scenario at 500rpm; this agitation speed should be avoided at the conditions (i.e. solid concentration and volume) considered. Hence, the increase in the total counts for the suspension can be related to mixing conditions. As the agitation speed increases, the system mixing improves and the probability to measure higher number of particles within the scanning time increases. Therefore, the total number of particles measured by the FBRM is proportional to the agitation speed for this system.

The effect of solid concentration on the FBRM statistics was investigated by adding 1g of beads in 300mL of water.. Figure 6a show the dynamic response of the FBRM statistics during the addition of a total of 10g of spherical glass beads in 1g intervals. The SWMCL dynamic profile shows significant noise at low solid concentrations (<0.67% w/w). The total count does not change linearly at 300rpm as observed in Figure B.4a-b. The linearity changes significantly after 4g of glass beads are added to the system (i.e. 13 mg/mL). This change in the linearity is not observed when the system is mixed at 400rpm. Hence, this change could be attributed to variations in the mixing behavior of the particles; it can be assumed that after 13mg/mL, the solid concentration is too high for a well-mixed system and some settling could be occurring. The increase in the total counts due to constant addition of particles decreases. Moreover, Figure B.4b shows that a higher variability on the average total counts at 400rpm. The variability of the average total counts also increased at higher concentration. This could be due to optical properties of the glass which creates higher variance in the measurement. The dynamic profile observed for the SWMCL shows that this measurement does not change with solid addition significantly for a well-mixed system (i.e. agitation speed of 400rpm). In this scenario, the solid mass of particles of specific size (i.e. d_{50} = 131μm) is increased and the SWMCL stays relatively constant (refer to Figure B.4c). However, the SWMCL is significantly affected by solid mass at 300rpm. Therefore, the batch system needs to be a well-mixed to avoid significant effect on the size and total counts measurements due to variations on only solid concentration.

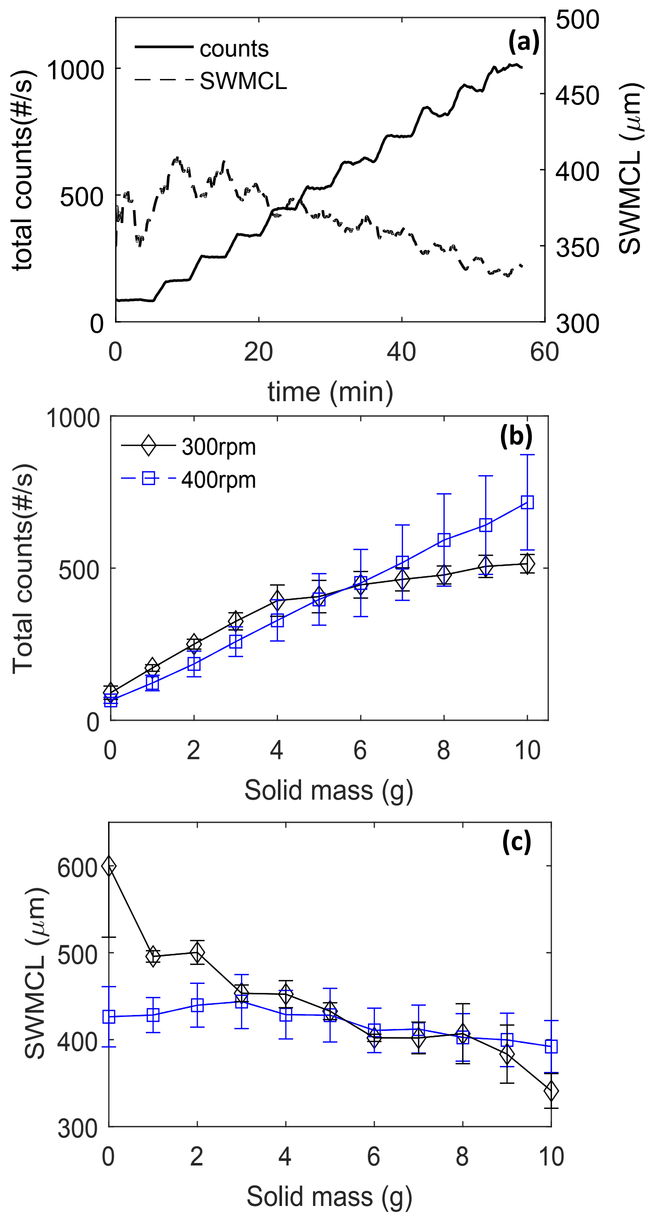


Figure B.4.. (a) Example of dynamic response of total counts and SWMCL for additions of 1g of spherical glass beads at 300rpm. Average (b) total counts, and (c) SWMCL for various amount of glass beads in suspension at 300 (diamond) and 400rpm (square).

Supplement C. Assessment of FBRM statistics for CBZ

C.1. Repeatability study with CBZ

The precision of FBRM measurements was assessed by monitoring seed crystals of two size ranges for a short period (i.e. < 5 min). A fixed amount of seed crystals (10mg/mL) were added to a saturated solution of CBZ (22.3 mg/mL) that was agitated at 400 rpm. The last six measurements (i.e. 1 min) were used for the evaluation of the precision within the same day of operation. The procedure was repeated three times on the same day. The intra-day study results for both size distributions considered are shown in Table C.1..

Table C.1. . Intra-day study with CBZ seed crystals in saturated solutions (i.e.22.3 mg/mL).

FBRM statistic	Trial	CSD: <75 µm (n= 18)				CSD: >212 µm (n=18)			
		Average	**Conf. Int.**	**RSD (%)**	**Overall RSD (%)**	**Average**	**Conf. Int.**	**RSD (%)**	**Overall RSD (%)**
SWMCL (µm)	1	111.19	0.11	0.12		262.31	0.55	0.26	
	2	111.95	0.12	0.14	0.95	268.16	0.77	0.36	1.33
	3	113.64	0.13	0.14		271.42	1.15	0.53	
Total counts (#/s)	1	3354.78	4.99	0.18		394.24	0.49	0.15	
	2	3356.67	3.87	0.14	4.13	405.39	0.39	0.12	1.95
	3	3225.87	2.13	0.08		412.83	0.77	0.23	

The average values for the SWMCL demonstrates small variation on the crystal size for both distributions. The RSDs within the six measurements considered for each trial are below 1%. This was also observed for the total counts RSD for each individual trial. The overall RSD considering the measurements of the three trials shows an RSD between 0.95 and 4.13%. The highest RSD obtained was for the total counts of the CSD < 75μm. This could be due to the high number of particles and high agitation used; an increase in the SWMCL in trial 3 is observed which could be due to small dissolution of fine particles (decrease in counts). This could contribute for the overall RSD to be higher than the RSD achieved for the set of larger seed crystals.

Further tests a wider range of seed crystals could be tested. Nonetheless, this study shows a possible dependency of the precision of FBRM measurements with particle size and type of measurement (SWMCL or total counts) for CBZ at the conditions evaluated. This type of study allows evaluating the inherent variance of the FBRM measurements for the API of interest (CBZ) since most of the conditions, expect particle size, were fixed. Moreover, it is shown that the precision is comparable to the assumed ideal scenario studied (i.e. spherical glass beads, refer to supplement B.2 for more details).

C.2. Impact of process variables on FBRM statistics

The impact of crystal size, solid concentration, and agitation speed on the FBRM measurements was assessed via a design of experiments. Various sieved seed crystals of various size ranges were monitored in a saturated solution. The system was mixed at various agitation speeds and monitored for a period of one hour. The temperature was controlled at 20°C which was the saturation temperature considered. Average FBRM statistics were calculated over the last 15 minutes for each experiment. The SWMCL, total counts and fouling index were considered as FBRM statistics of interest due to the direct correlation to crystal size, solid concentration, and possible probe fouling. The average mean size (d_{50}) of each set of sieved crystals was used to describe the impact of crystal size for the statistical analysis.

The unbalance fractional factorial design was analyzed using MiniTab. A detailed summary of the statistical and average FBRM statistics values can be found in supplementary documents. In this scenario, only two factors (crystal size and solid concentration) have a significant effect on the measured SWMCL as observed by the large standardized effect which are above the critical value estimated from the statistical analysis. Moreover, a significance difference can be observed between the impact of the crystal size and solid concentration; the SWMCL is mainly affected by the size of the particles in the system. This is an expected observation since the SWMCL is a measure of the mean chord length of the measured particles. Nonetheless, the impact of solid concentration on the SWMCL shows that there is an effect on the measured size. Previously, it was shown that there is some effect of solid concentration on the measured SWMCL (refer to Supplement B.2). A slight decrease on the measured SWMCL was observed as the solid concentration increased. Higher SWMCL is observed at low solid concentration, this could be related to possible noise.

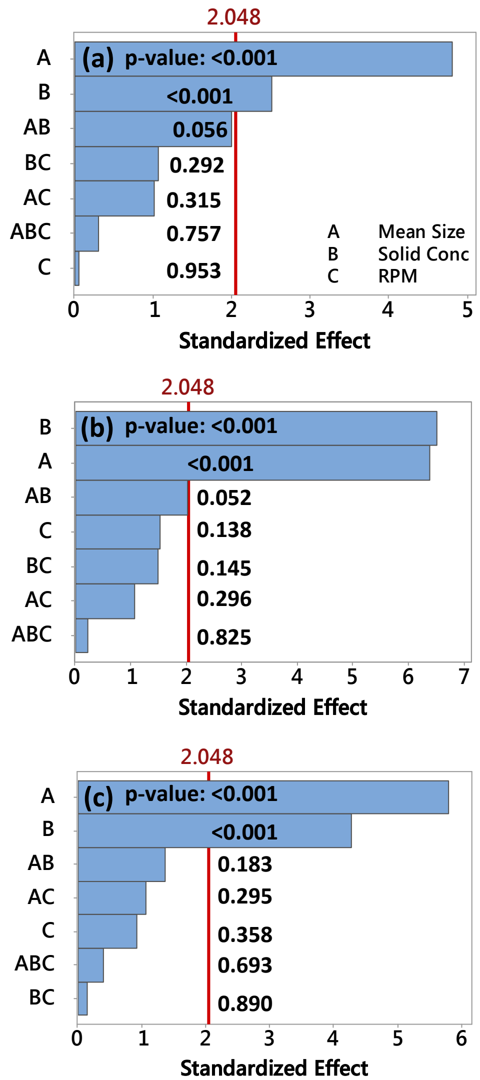


Figure C.1.. Standardize effect for mean size (d_{50}, μm), solid concentration (mg/mL), and agitation speed (RPM) on (a) SWMCL (μm), (b) total counts (#/s), and (c) FI (%).

The analysis of standardize effects such as crystal size, solid concentration, and agitation speed on the total counts measured and fine index (FI) is shown in FigureC.1b-c. For both scenarios, it is observed that only the crystal mean-size and solid concentrations have significant impact on the statistics. The p-values are below the significance level and the standardized effect is above the critical limit (2.048). The effect of crystal size and solid concentration on the total counts is almost similar as observed from the standardized effects. Moreover, the two-way interaction between these two factors is almost at the significance level set for the statistical analysis. This effect was observed during the intra-day precision study in which two crystal size ranges were evaluated. A lower count was achieved for the scenario in which coarse crystals were analyzed (refer to Table C.1.). At a fixed solid concentration, a lower number of coarse crystals are necessary to achieve the desired mass. Hence, the total counts measured are affected by the solid concentration and crystal since the number of particles in the system are correlated to the crystal size for a specific concentration. A similar behavior is observed for the FI%, which can be used as an indication of fouling in the probe window. A higher number of particles and crystal size would result in a high FI% since a higher number of the probe window is being used for measurement in one scan. Nonetheless, a maximum FI% was estimated under normal operating conditions within the ranges considered. Figure C.2 shows a response surface plot generated from the statistical analysis of FI% variation with mean crystal size (d_{50}), solid concentration at fixed agitation speed (i.e. 300rpm). It can be observed that the maximum FI% expected is around 4.5%. Hence, a FI of 5% would be consider as limit for probe cleaning procedures in future batch and continuous cooling crystallization operations.

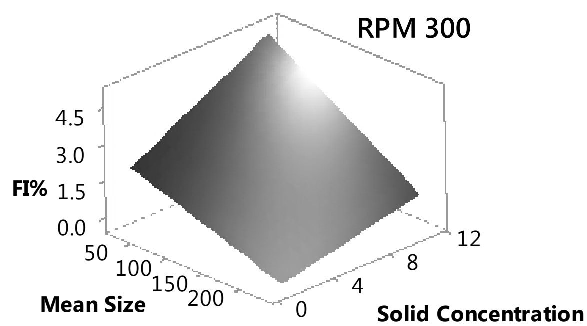


Figure C.2. Response surface plot for FI% at fixed agitation speed (i.e. 300rpm) for various solid concentrations (mg/mL) and mean size (d_{50}, μm).

The agitation speed does not have significant effect on any of the FBRM statistics (SWMCL, total counts, and FI) considered with the solid concentration and particle size considered. This can indicate that the system is well-mixed within the range considered due to the CBZ density is closer to ethanol than ideal system such as glass beads. Nonetheless, other type of analysis and estimation should be performed to validate this observation. Previous work showed that this agitation speed results in a well-mixed system for CBZ in our 400mL crystallizer.[51] Hence, agitation speed should not have a significant impact on the FBRM statistics for this system. This assumption is only valid for the solid concentration and particle size ranges considered and further studies should be performed for scenarios out of this range. This study demonstrated that only solid concentration and crystal size have a significant impact on the FBRM statistics considered for the range considered. No two-way or three-way interactions were statistically significant. Moreover, a cleaning procedure was formulated by assuming a maximum fouling index under normal operating conditions. This will be beneficial for batch and continuous cooling crystallization operations for CBZ in future work.

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