Examination of a time release OTC drug by laser diffraction particle size measurement and image analysis

Instrument: SYNC

SL-AN-61 Rev. C

Introduction

Modified release dosage form refers to a measured delay on release of drug after it is consumed orally. It prolongs the effect of the drug so that multiple doses are not necessary. There are several terms available to describe “Timed Release Drugs” such as sustained release, prolonged release and delayed response and controlled release. Sustained forms are designed to release the drug at a specified rate to maintain concentration with minimum side effects. (Liposomes represents one form of such release control. For information on liposome measurements please see Microtrac.com Applications Note SL-AN-07 “High-Concentration Liposome and Micelle Suspensions: Measurement by Dynamic Light Scattering”.). The sustained release provides immediate release of drug for rapid effect and then is followed by slow release of the remaining dosage. Levels of drug are prolonged, but concentrations are not maintained constant. On the other hand, Controlled Release is designed to provide constant release and maintain concentrations over time and apply therapeutic action at a specific site. Sustained release can be considered Controlled release depending on the purpose and properties.

Hydroxypropylmethylcellulose is usually used as the capsule information. It provides a hydrophilic barrier that can expand when n contact with aqueous environment. The expansion of the polymer provides a portion of the phenomenon of release control since water can enter the capsule and start a dissolution of the drug which diffuses out of the capsule. Insoluble components remain within the capsule until complete dissolution of the polymer has occurred. There the system provides a systematic approach whereby the capsule wets, hydrates and finally dissolves while simultaneously various drugs are released by diffusion through the hydrated gel or after complete dissolution of the capsule.

The present experiments describe information obtained on a timed-release OTC anti-heartburn medication. For purposes of the experiment, the capsule was gently cut in half to release the contents of the capsule. Several capsules were used for each experiment. Measurements were performed simultaneously using the Microtrac Sync combined laser diffraction particle size and image analysis instrumentation. Effect on size and shape were evaluated as well as the ability to elucidate the ability of the instruments to assist understanding the mechanism of dissolution of the drug “beads”.

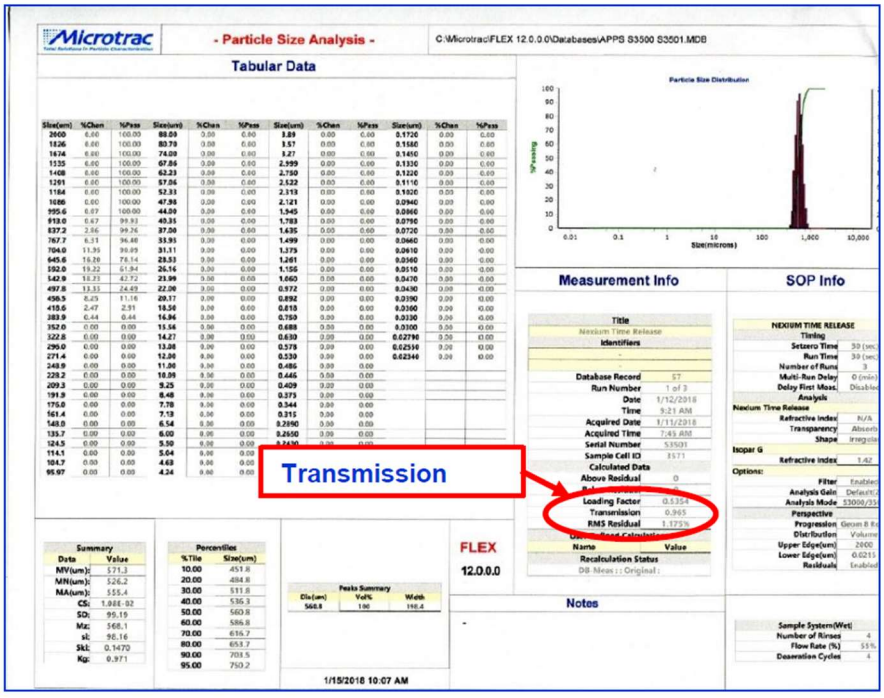
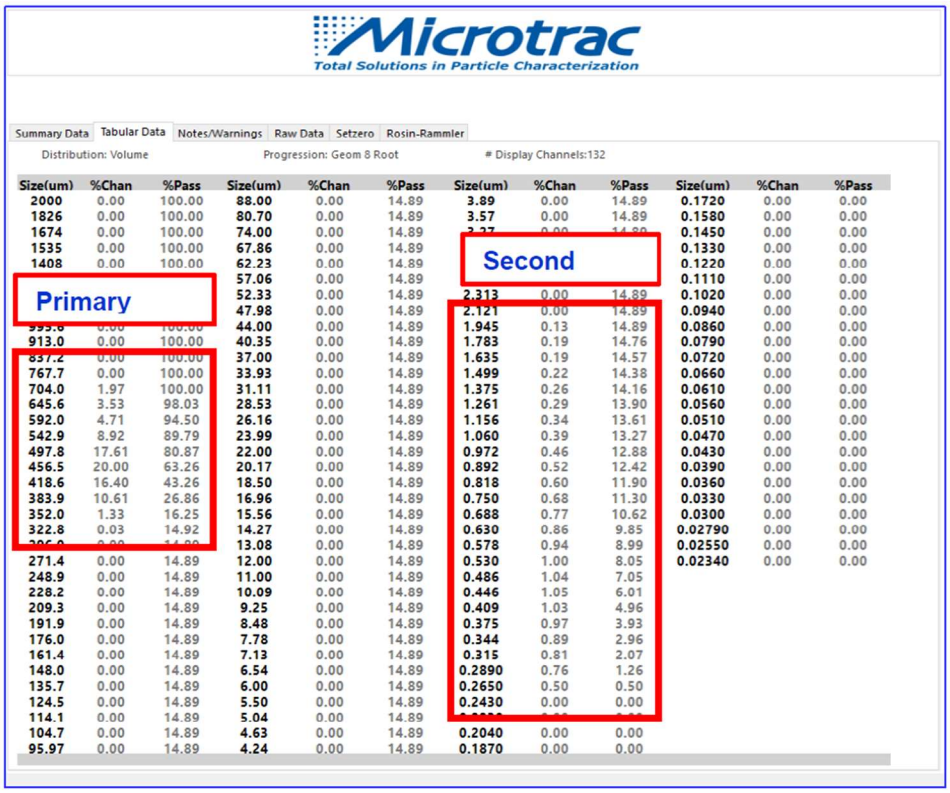


Figure 1: *Microtrac SYNC diffraction distribution for beads measured in ISOPAR G. Transmission value shows that 96 % of the laser light is passing through the optical system. Transmission increases with smaller amounts of sample particles.*

Data and Results

Figure 1 is a Sync diffraction printout showing the size measurement when the beads are measured in Isopar G. Isopar G provides a medium in which aqueous soluble particles are not soluble. Figure 2 shows the effects of mixing with water and agitation by the Sync circulation system, Measurements were taken at 45 second intervals during a total time period 4 minutes.



Microtrac
Total Solutions in Particle Characterization

Summary Data | Tabular Data | Notes/Warnings | Raw Data | Setzero | Rosin-Rammler

Distribution: Volume Progression: Geom 8 Root # Display Channels:132

Size(um)	%Chan	%Pass	Size(um)	%Chan	%Pass	Size(um)	%Chan	%Pass	Size(um)	%Chan	%Pass
2000	0.00	100.00	88.00	0.00	14.89	3.89	0.00	14.89	0.1720	0.00	0.00
1826	0.00	100.00	80.70	0.00	14.89	3.57	0.00	14.89	0.1580	0.00	0.00
1674	0.00	100.00	74.00	0.00	14.89				0.1450	0.00	0.00
1535	0.00	100.00	67.86	0.00	14.89				0.1330	0.00	0.00
1408	0.00	100.00	62.23	0.00	14.89				0.1220	0.00	0.00
			57.06	0.00	14.89				0.1110	0.00	0.00
			52.33	0.00	14.89	2.313	0.00	14.89	0.1020	0.00	0.00
			47.98	0.00	14.89	2.121	0.00	14.89	0.0940	0.00	0.00
			44.00	0.00	14.89	1.945	0.13	14.89	0.0860	0.00	0.00
913.0	0.00	100.00	40.35	0.00	14.89	1.783	0.19	14.76	0.0790	0.00	0.00
			37.00	0.00	14.89	1.635	0.19	14.57	0.0720	0.00	0.00
767.7	0.00	100.00	33.93	0.00	14.89	1.499	0.22	14.38	0.0660	0.00	0.00
704.0	1.97	100.00	31.11	0.00	14.89	1.375	0.26	14.16	0.0610	0.00	0.00
645.6	3.53	98.03	28.53	0.00	14.89	1.261	0.29	13.90	0.0560	0.00	0.00
592.0	4.71	94.50	26.16	0.00	14.89	1.156	0.34	13.61	0.0510	0.00	0.00
542.9	8.92	89.79	23.99	0.00	14.89	1.060	0.39	13.27	0.0470	0.00	0.00
497.8	17.61	80.87	22.00	0.00	14.89	0.972	0.46	12.88	0.0430	0.00	0.00
456.5	20.00	63.26	20.17	0.00	14.89	0.892	0.52	12.42	0.0390	0.00	0.00
418.6	16.40	43.26	18.50	0.00	14.89	0.818	0.60	11.90	0.0360	0.00	0.00
383.9	10.61	26.86	16.96	0.00	14.89	0.750	0.68	11.30	0.0330	0.00	0.00
352.0	1.33	16.25	15.56	0.00	14.89	0.688	0.77	10.62	0.0300	0.00	0.00
322.8	0.03	14.92	14.27	0.00	14.89	0.630	0.86	9.85	0.02790	0.00	0.00
			13.08	0.00	14.89	0.578	0.94	8.99	0.02550	0.00	0.00
271.4	0.00	14.89	12.00	0.00	14.89	0.530	1.00	8.05	0.02340	0.00	0.00
248.9	0.00	14.89	11.00	0.00	14.89	0.486	1.04	7.05			
228.2	0.00	14.89	10.09	0.00	14.89	0.446	1.05	6.01			
209.3	0.00	14.89	9.25	0.00	14.89	0.409	1.03	4.96			
191.9	0.00	14.89	8.48	0.00	14.89	0.375	0.97	3.93			
176.0	0.00	14.89	7.78	0.00	14.89	0.344	0.89	2.96			
161.4	0.00	14.89	7.13	0.00	14.89	0.315	0.81	2.07			
148.0	0.00	14.89	6.54	0.00	14.89	0.2890	0.76	1.26			
135.7	0.00	14.89	6.00	0.00	14.89	0.2650	0.50	0.50			
124.5	0.00	14.89	5.50	0.00	14.89	0.2430	0.00	0.00			
114.1	0.00	14.89	5.04	0.00	14.89						
104.7	0.00	14.89	4.63	0.00	14.89	0.2040	0.00	0.00			
95.97	0.00	14.89	4.24	0.00	14.89	0.1870	0.00	0.00			

Primary

Second

Figure 2: *Microtrac Sync Diffraction Distribution for beads measured in water. Shows two groups (peaks) of particles produced by mixing in water.*

The data show an immediate release of particulate of small size noticeable by the second peak in the distribution. The particles in the second peak range in size from approximately 0.25µm to 2µm which is well within the capability of Microtrac Sync laser diffraction technology which can measure particles as small as 0.010µm (10nm). As time progresses the amount of the finer peak decreases until complete dissolution occurs as shown in Figure 3 and 4. The blue colored curve (agitation duration approximately 4 minutes) shows larger size particulate only. The disappearance can also be tracked by noting the transmission value and signal displayed by the diffraction data. Signal decreases while transmission increases. Higher light transmission is an indicator of how much of the original laser intensity is not being scattered by the particles passing through the circulation system. Thus, as particulate concentration increases, less of the original laser persists since more light scattering occurs.

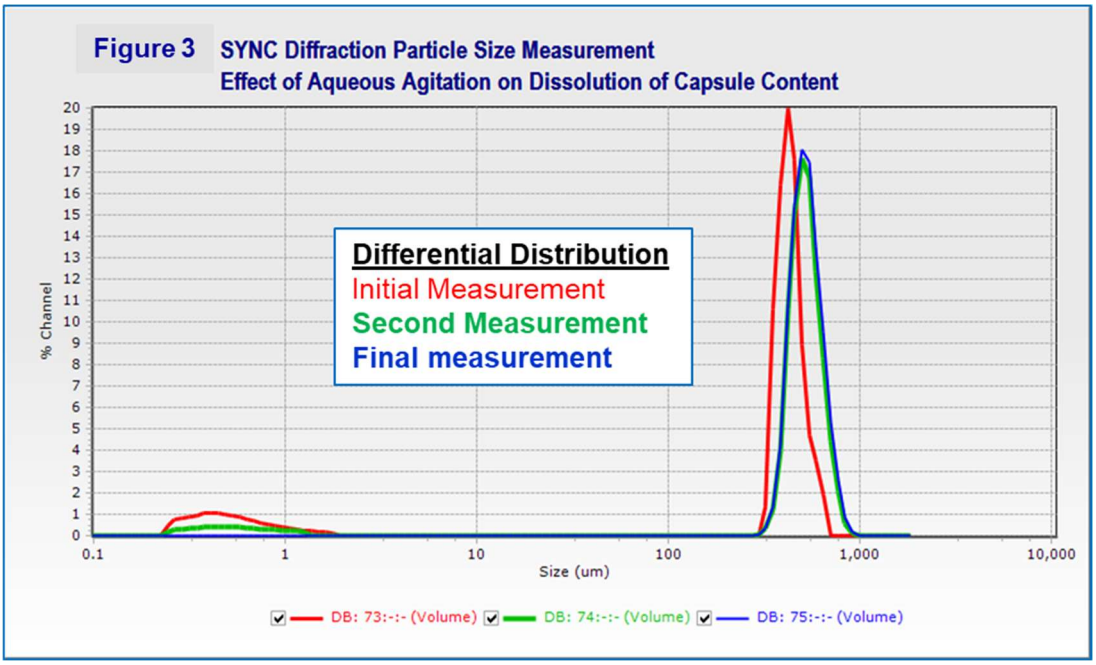


Figure 3. *Sync diffraction particle size measurement: Effect of Aqueous Agitation on Dissolution of Capsule Content*

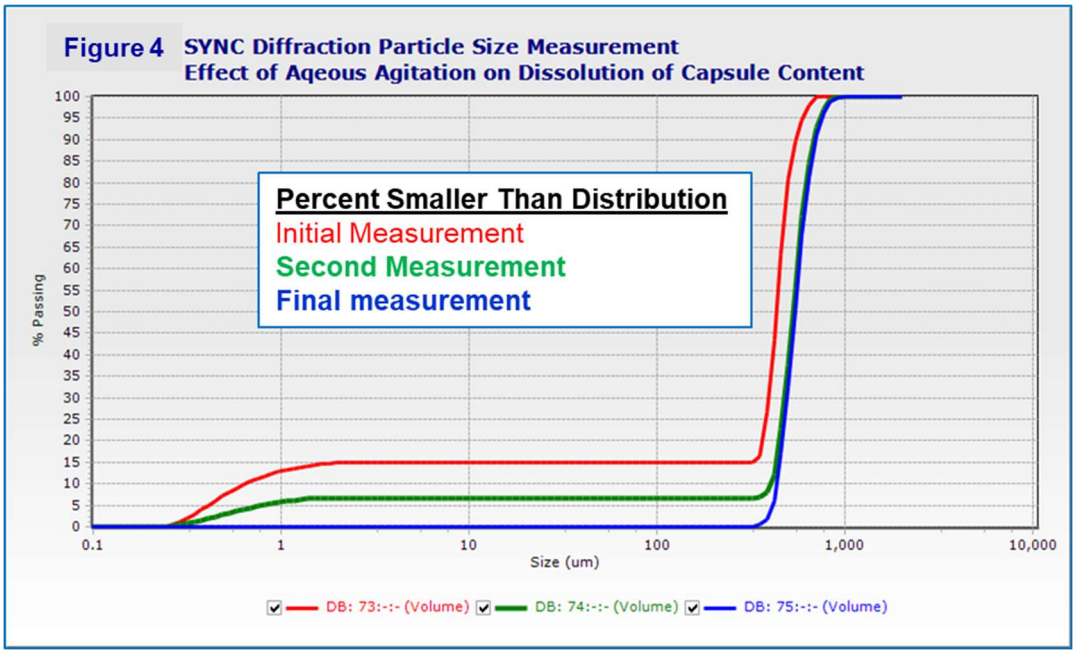
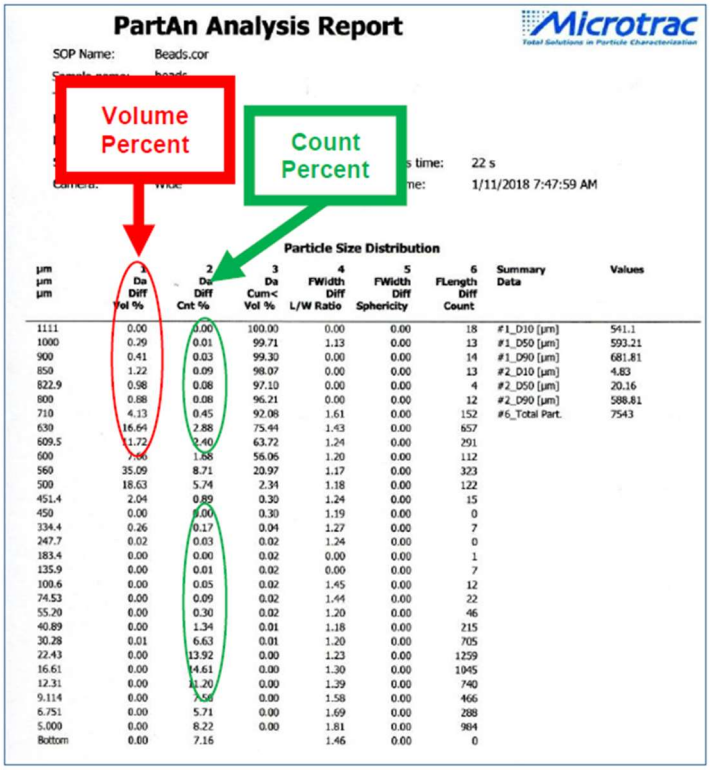


Figure 4. *Sync diffraction particle size measurement: Effect of Aqueous Agitation on Dissolution of Capsule Content*

Sync image analysis shows similar trend of information. Of special interest is columns 1 and 2 in Figure 5 showing a comparison of volume and number distributions for Da (Area Equivalent Diameter). Number shows presence of finer particles observed as a very small volume contribution as expected based on volume/number relationships. Indication of finer particle presence is shown by the graph in Figure 6 and the scatter diagram in Figure 7. The scatter diagram is especially interesting since volume and number distribution for the applicable image range is shown. As shown in the image tabular data, the number scatter diagram shows a second peak while the Da presented as a volume distribution does not show the second peak. This is normal for a bimodal distribution because of the mathematical relationship between number of particles and volume of those particles.



PartAn Analysis Report

Microtrac

SOP Name: Beads.cor

Volume Percent

Count Percent

s time: 22 s

me: 1/11/2018 7:47:59 AM

Particle Size Distribution

µm µm µm	1 Da Diff Vol %	2 Da Diff Cnt %	3 Da Cum< Vol %	4 FWidth Diff L/W Ratio	5 FWidth Diff Sphericity	6 FLength Diff Count	Summary Data	Values
1111	0.00	0.00	100.00	0.00	0.00	18	#1_D10 [µm]	541.1
1000	0.29	0.01	99.71	1.13	0.00	13	#1_D50 [µm]	593.21
900	0.41	0.03	99.30	0.00	0.00	14	#1_D90 [µm]	681.81
850	1.22	0.09	98.07	0.00	0.00	13	#2_D10 [µm]	4.83
822.9	0.98	0.08	97.10	0.00	0.00	4	#2_D50 [µm]	20.16
800	0.88	0.08	96.21	0.00	0.00	12	#2_D90 [µm]	588.81
710	4.13	0.45	92.08	1.61	0.00	152	#6_Total Part.	7543
630	16.64	2.88	75.44	1.43	0.00	657		
609.5	11.72	2.40	63.72	1.24	0.00	291		
600	7.66	1.88	56.06	1.20	0.00	112		
560	35.09	8.71	20.97	1.17	0.00	323		
500	18.63	5.74	2.34	1.18	0.00	122		
451.4	2.04	0.89	0.30	1.24	0.00	15		
450	0.00	0.00	0.30	1.19	0.00	0		
334.4	0.26	0.17	0.04	1.27	0.00	7		
247.7	0.02	0.03	0.02	1.24	0.00	0		
183.4	0.00	0.00	0.02	0.00	0.00	1		
135.9	0.00	0.01	0.02	0.00	0.00	7		
100.6	0.00	0.05	0.02	1.45	0.00	12		
74.53	0.00	0.09	0.02	1.44	0.00	22		
55.20	0.00	0.30	0.02	1.20	0.00	46		
40.89	0.00	1.34	0.01	1.18	0.00	215		
30.28	0.01	6.63	0.01	1.20	0.00	705		
22.43	0.00	13.92	0.00	1.23	0.00	1259		
16.61	0.00	14.61	0.00	1.30	0.00	1045		
12.31	0.00	11.20	0.00	1.39	0.00	740		
9.114	0.00	7.58	0.00	1.58	0.00	466		
6.751	0.00	5.71	0.00	1.69	0.00	288		
5.000	0.00	8.22	0.00	1.81	0.00	984		
Bottom	0.00	7.16		1.46	0.00	0		

Figure 5. *Sync Image Analysis tabular data for several parameters.*

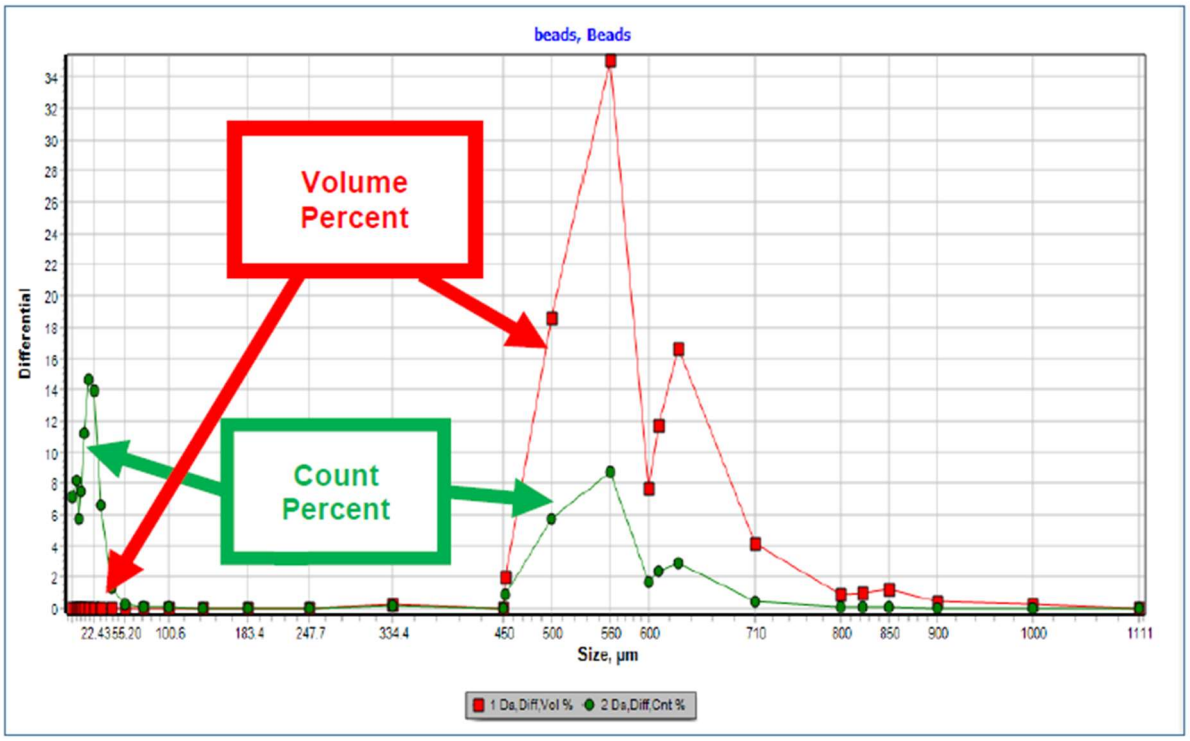


Figure 6. *SYNC Image analysis graph showing small volume amount of fines (in the third decimal place). Demonstrates the use of number distributions to report very small volume presence.*

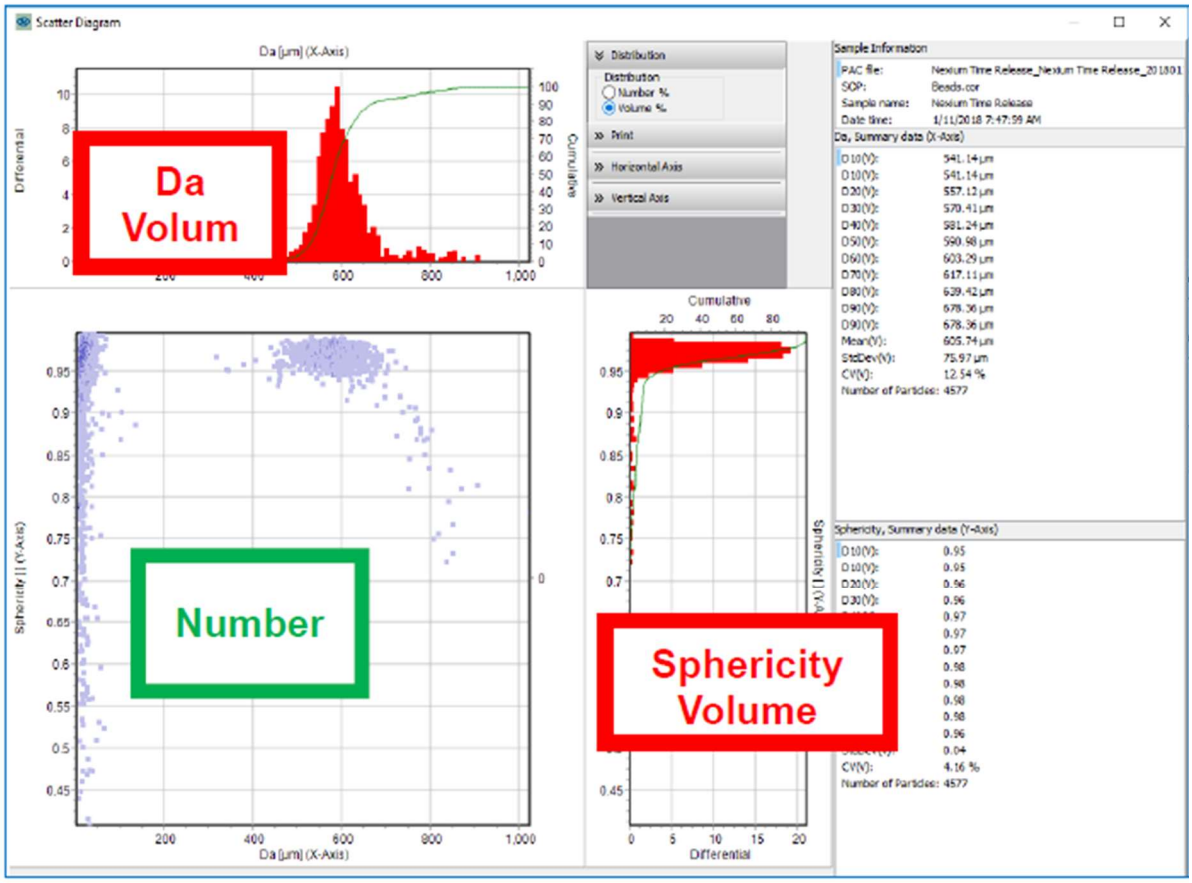
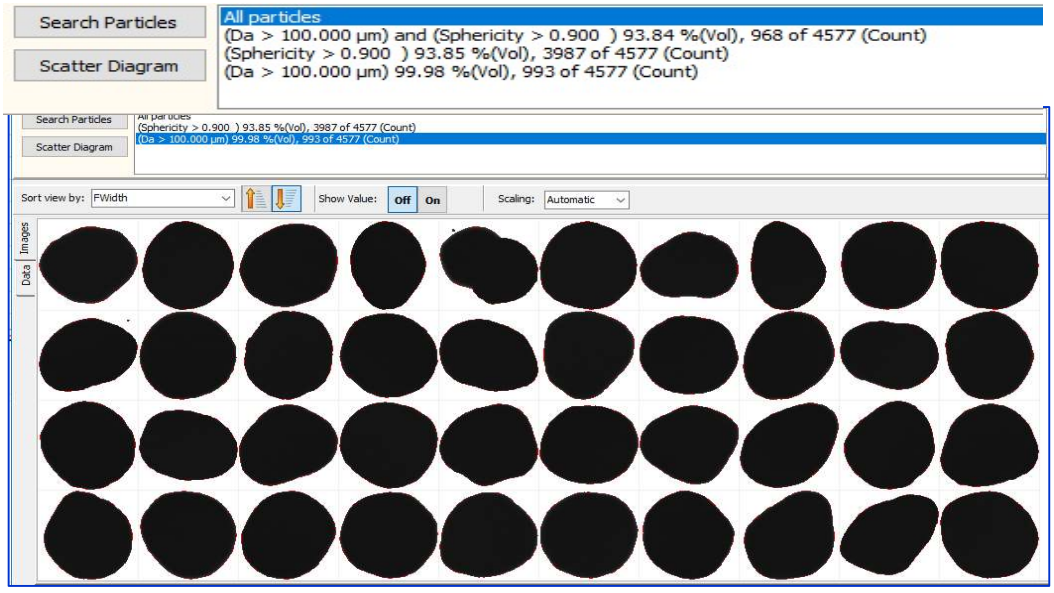


Figure 7. *Sync Image Analysis scatter diagram. Using volume for size and shape allows special comparisons. (1) Comparison to number distribution in the scatter plot. (2) Percentile information in either number or volume format. (3) Evaluation of volume (weight) concentration relative to size. (4) Shape information related to size/volume distribution.*



According to the Sync image analysis "Search" function, various types of information can be elucidated. A search of all particles for those having a sphericity of greater than 0.9 represents 93.85% volume and 87% [100 (3987/4577)] of the total number of particles. Similarly, the volume percent of particles larger than 100µm is 99.98% while representing 21% [100 (993/4577)] of the number of particles. Particles that are larger than 100µm having a sphericity greater than 0.9 is calculated as 93.84%. These volumes (weights) may provide a starting point for establishing specifications for manufacturing or quality purposes.

The images shown in the picture below in Figure 8 show particles nearing the limits of view in the range less than 2-5um. The particle shapes are similar to those observed for the particles representing the larger particles. Image analysis is not available for the very fine particles reported by laser diffraction measurement. Note that some particles are not "round" and have a low width/length aspect ratio which may be indicative of particle attrition or disrupture. Particles smaller than 100µm represent 0.45% of the total volume.

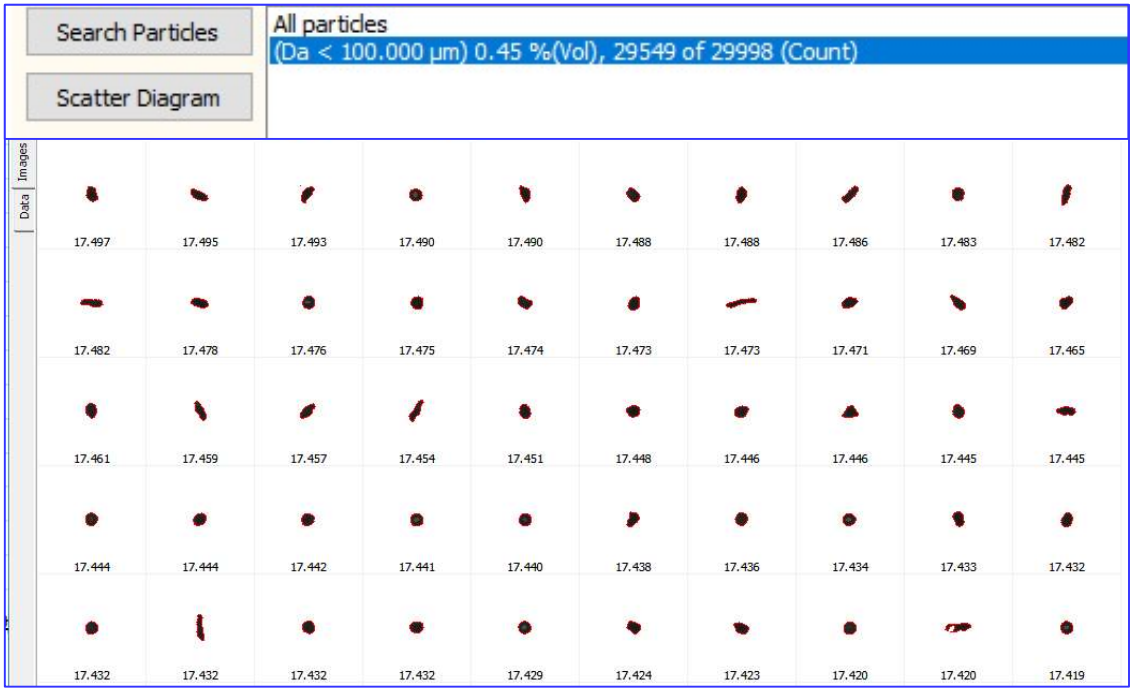


Figure 8. *Particles represented by the peak at the smaller sizes*

	Diffraction	Image Analysis
Volume (Large sizes peak)	86% 325 – 770µm	100% 450 - 1000µm
Volume (Small size peak)	14% Less than 100um Actual range 0.25 – 2µm	0% Less than 100µm
Number (Large sizes peak)	0% (Laser diffraction does not count particles).	22% 450 - 1000µm
Number (Large sizes peak	100% Smaller than 2µm	78% 5 – 55µm

Table 1. *Comparison of image analysis and diffraction particle size distributions.*

Summary

Diffraction particle size measurement and image analysis provide data and information that are very valuable in establishing specifications and limits for production and quality control. They both can provide insight into R&D projects or process issues. It is important to note that the methods have an entirely different approach to measurement and thus the capabilities of each is slightly different. (Diffraction uses an ensemble technique where a cloud of particles interacts with a laser beam. Image analysis captures photos of individual particles and performs geometric calculations on the images captured.). This difference in capability is very important, since the difference allows a deeper analysis than either of them separately. Thus, the simultaneous (not sequential) measurement by diffraction and imaging provides a synergistic effect, where the combination of techniques is greater than the sum, by combining image single particle analysis with light scattering diffraction (cloud of particles).

The value of the analysis by the two methods is shown by the data in Table 1. Particle presence is shown by both methods within similar ranges when an overlapping size range is available. This is evident by considering the volume distributions for the larger particle peak. The range of sizes is similar, when measurable sizes are similar.

Because size measuring capability is different for the two, divergence of volume and number distribution data occurs. This is also observable in the data. Imaging is not always capable of measuring particles that are within the capability of laser light diffraction. Thus, the peak that represents the smaller particles is only fully represented by diffraction. However, most of the weight in the product is governed by the larger particles even though fewer in number. Since the particles are very much different in size (large particle peak and small particle peak), then segregation can occur as the material is transported within production or among locations. The shape is important in this consideration since more spherically shaped particles tend to segregate more easily than non-spheres. Knowledge of the very fine size peak (identified by diffraction) is important for any materials that are to be ingested and experience physiological absorption since size contributes to the expected characteristics.

Generally, each method has capabilities that the other does not. However, the synergistic effect offered by the combination allows much greater characterization than either alone.