Elan Drug Technologies

Particle Size Method Development and Validation in Support of NanoCrystal Colloidal Dispersion® Formulation Characterization

Webinar Sponsored By:

HORIBA Scientific

August 2010
Joost Strasters

Overview

- Background: NanoCrystal Colloidal Dispersion® Compositions
- Relevance of particle size analysis
- Particle size method development and validation

Background

- Advances in Drug Discovery (e.g. High Throughput Screening) produce 30%-50% poorly water soluble leads
- Formulation Approaches Inadequate to Overcome:
  - Poor Bioavailability
  - Food Effects
  - Slow Absorption
  - Safety Issues for IV

Elan Drug Technologies

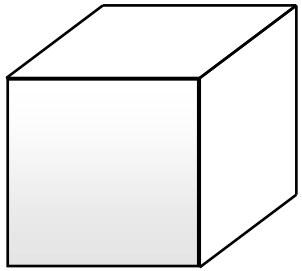
A proprietary formulation and manufacturing approach for the delivery of poorly water- soluble drugs

- Most dosage forms possible (e.g. oral, parenteral and nasal)
- Increases oral bioavailability & fed/fasted variability
- Decreases time to onset of action
- High drug loading possible (up to 30-40% active)
- Combine with other technologies (e.g. controlled release)
- Low viscosity liquid preparations
- Potential for improved chemical stability compared to solutions
- Uses standard pharmacopoeial materials

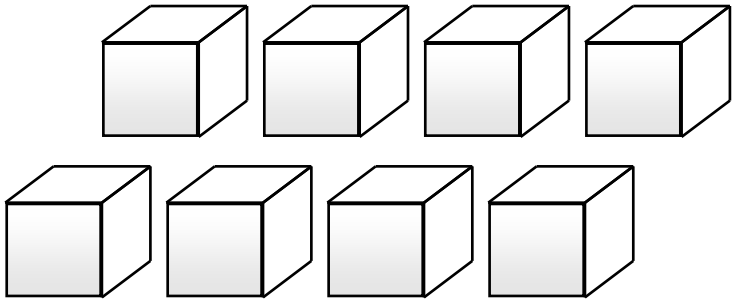
NanoCrystal® technology involves reducing drug particles to the nanometer size. By reducing particle size, we increase the drug's exposed surface area. We then stabilise the particles to maintain the formulation's particle size.

NanoCrystal® Particles Increase Surface Area

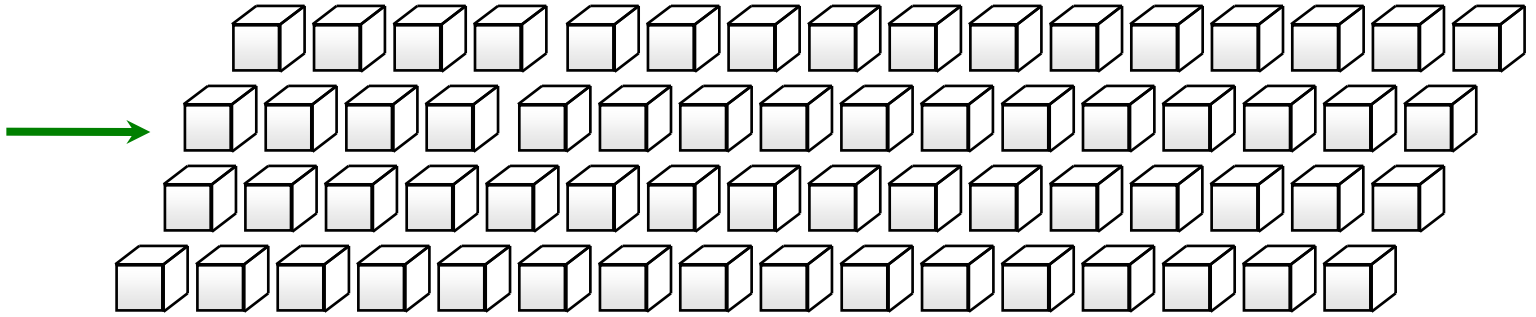
Total surface area
6 square inches



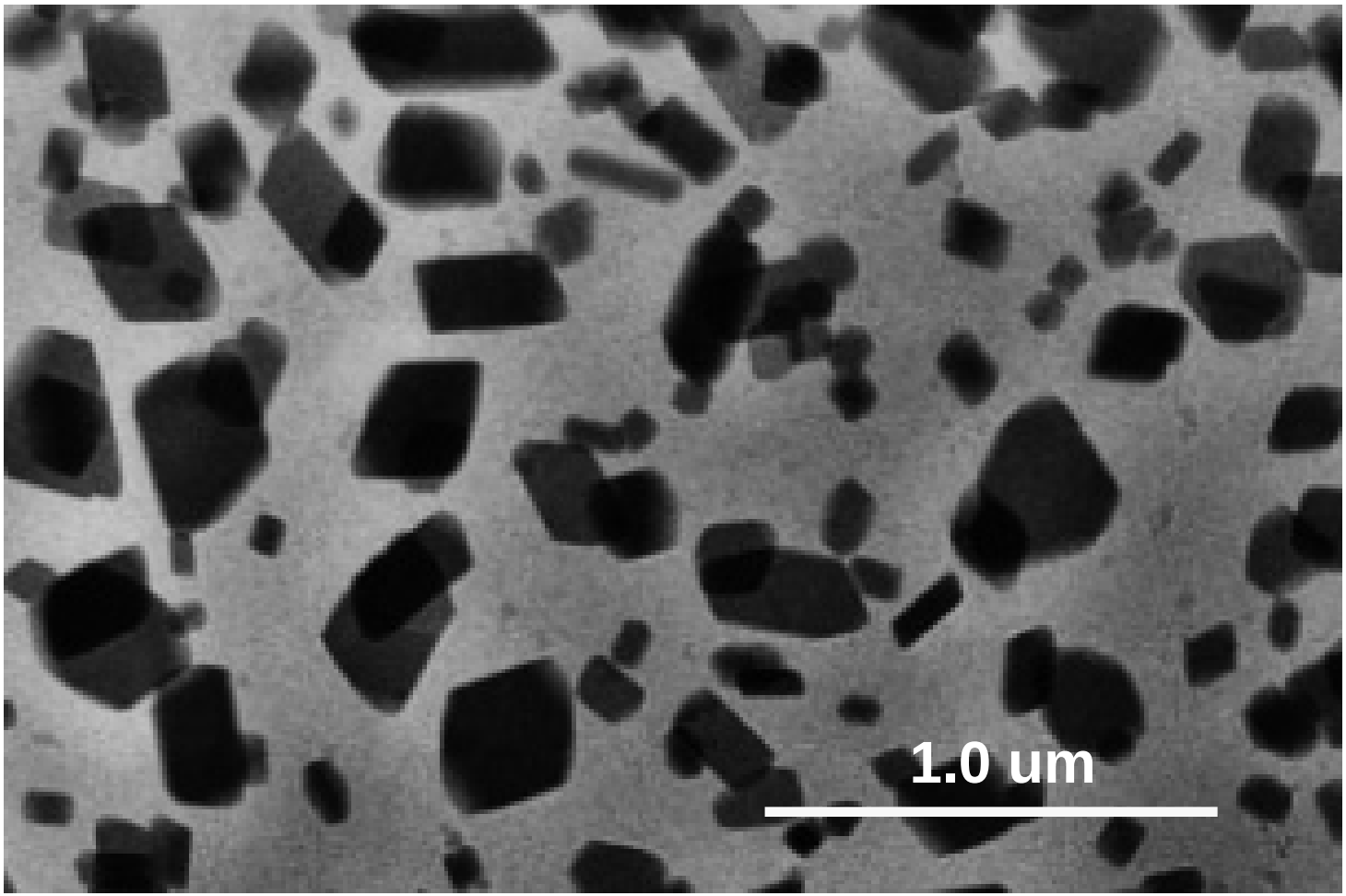
Total surface area
12 square inches



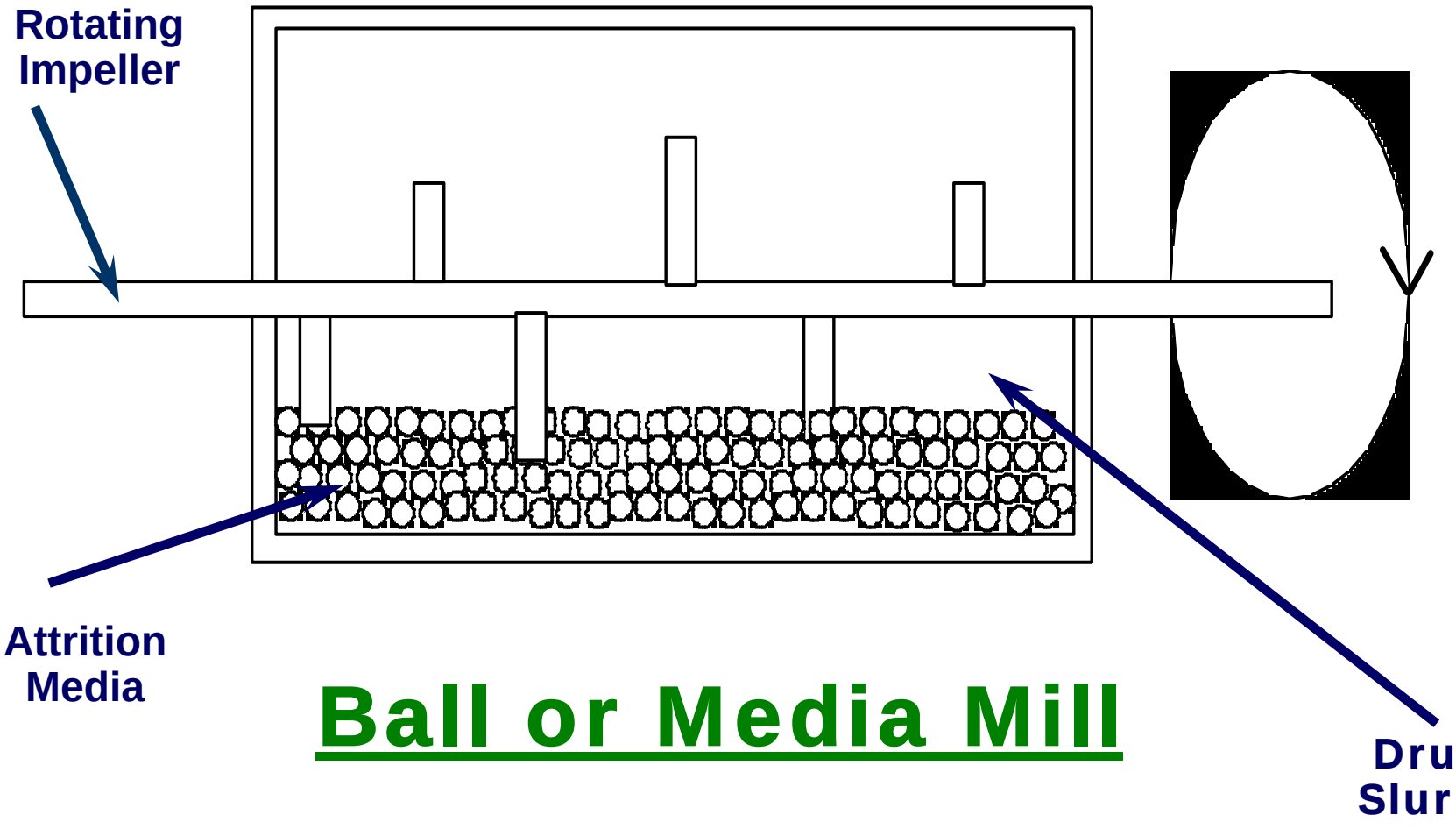
Total surface area
24 square inches



Morphology of NanoCrystal® Suspensions



How are they Made?



Ball or Media Mill

NanoCrystal® Technology

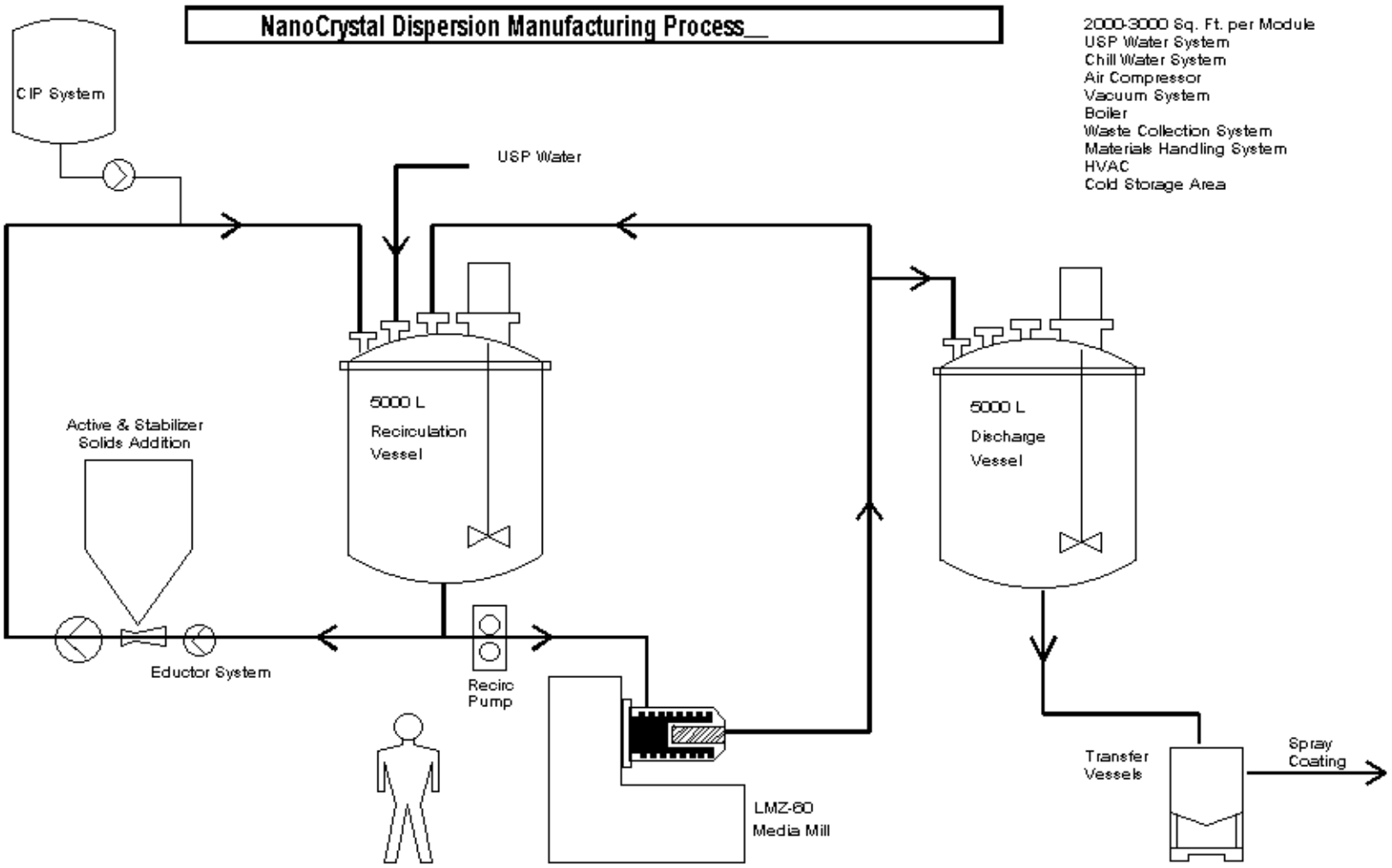
- Stable nanoparticles of poorly soluble drugs typically less than 2,000 nanometres (nm) in diameter
- can be produced using various approaches such as wet milling, homogenisation, precipitation and supercritical fluid techniques.
- The wet-milling size reduction process utilizes high energy ball milling with agitator bar
- Wide range of stabilizers including surfactants and polymers
- Worked on a broad range of insoluble actives

NanoMill® Media Mill 0.3L

NanoMill® Zeta Mill 10L

Elan Drug Technologies

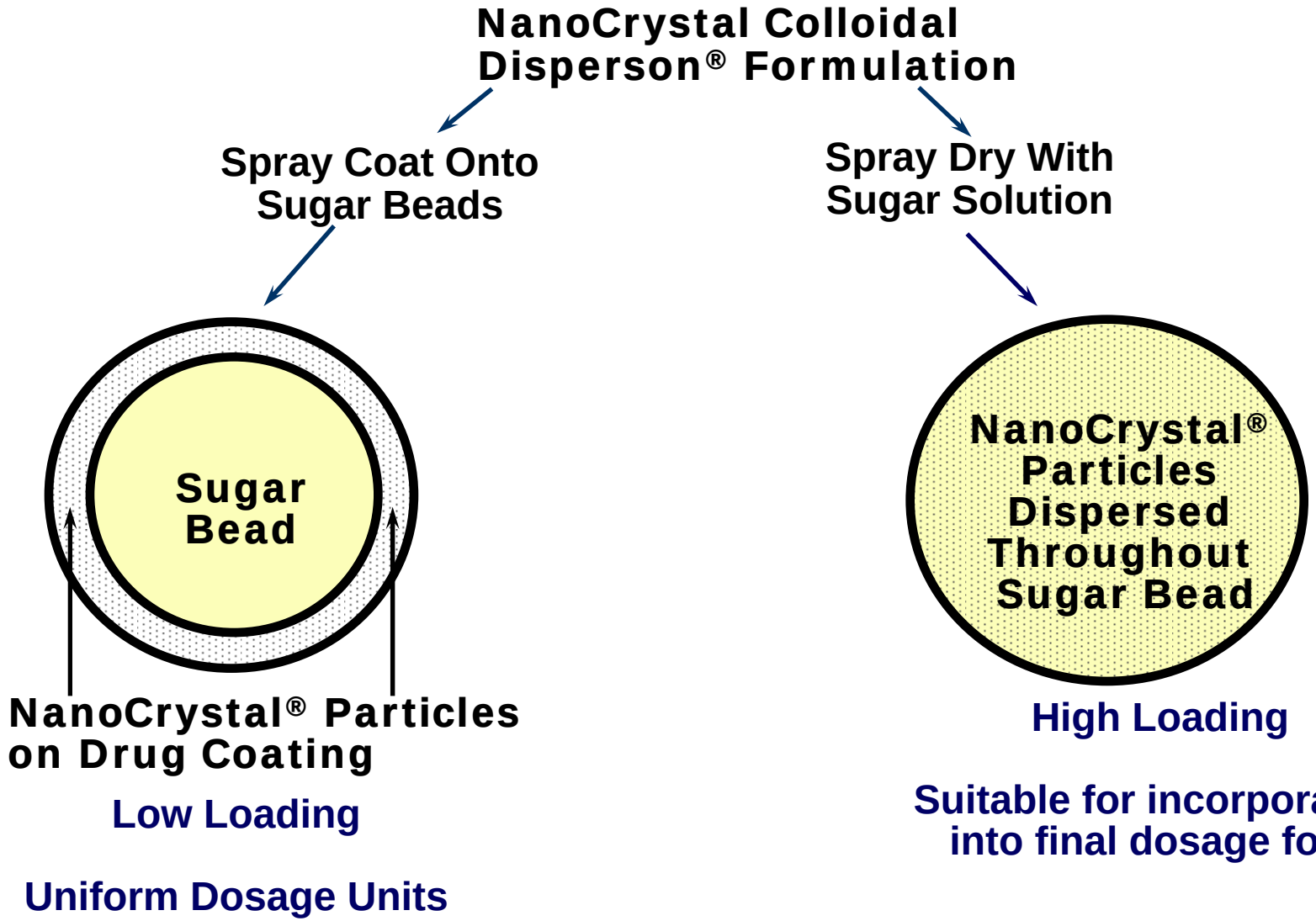
NanoCrystal Colloidal Dispersion® Manufacturing Process



Equipment vs. Development Stage

Stage	Mill	Min. API required per batch (kg)
Phase I	NanoMill®-Z2	1
Phase II	NanoMill®-Z10	5-10
Phase III	NanoMill®-Z10/ NanoMill®-Z60	5-10 50-100
Commercial	NanoMill®-Z60	1000

NanoCrystal Colloidal Dispersion® formulation to Solid Dosage Form



Particle size characterization

- static light scattering (laser diffraction)
- emphasis on precision

Solid dosage forms: dissolution vs. re-dispersability

Characterization of Particle Size Distributions

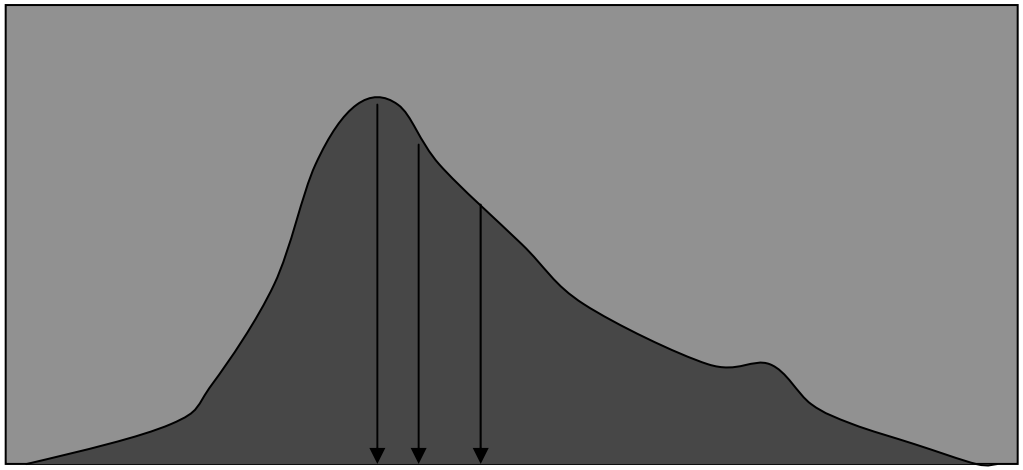
Elan Drug Technologies

Summarize observed distribution with a small number of characteristic values:

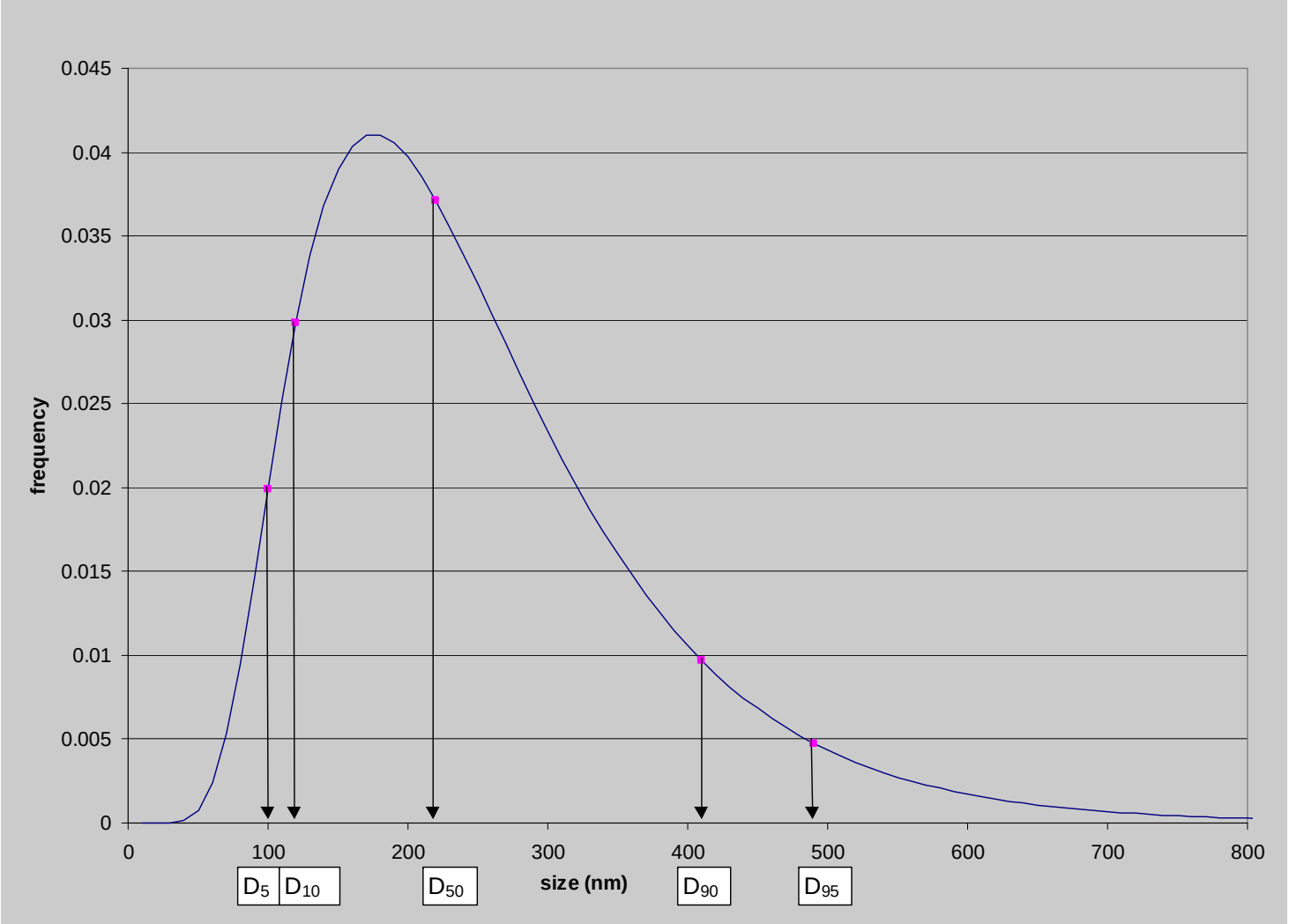
1) D_{mean}; mean diameter, center of gravity

2) Mode; diameter corresponding to maximum

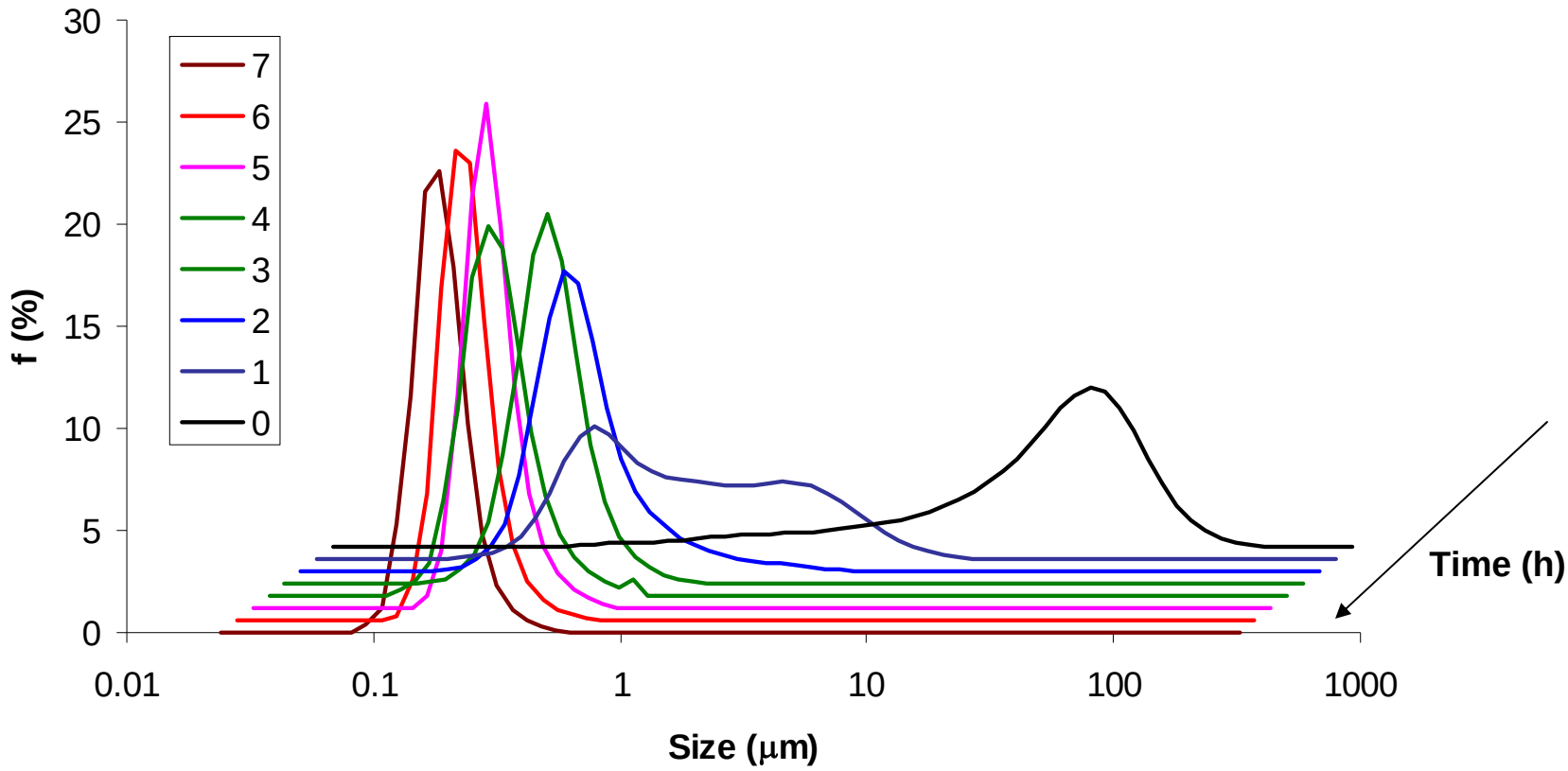
3) Median; 50% point (50% of area above and below)



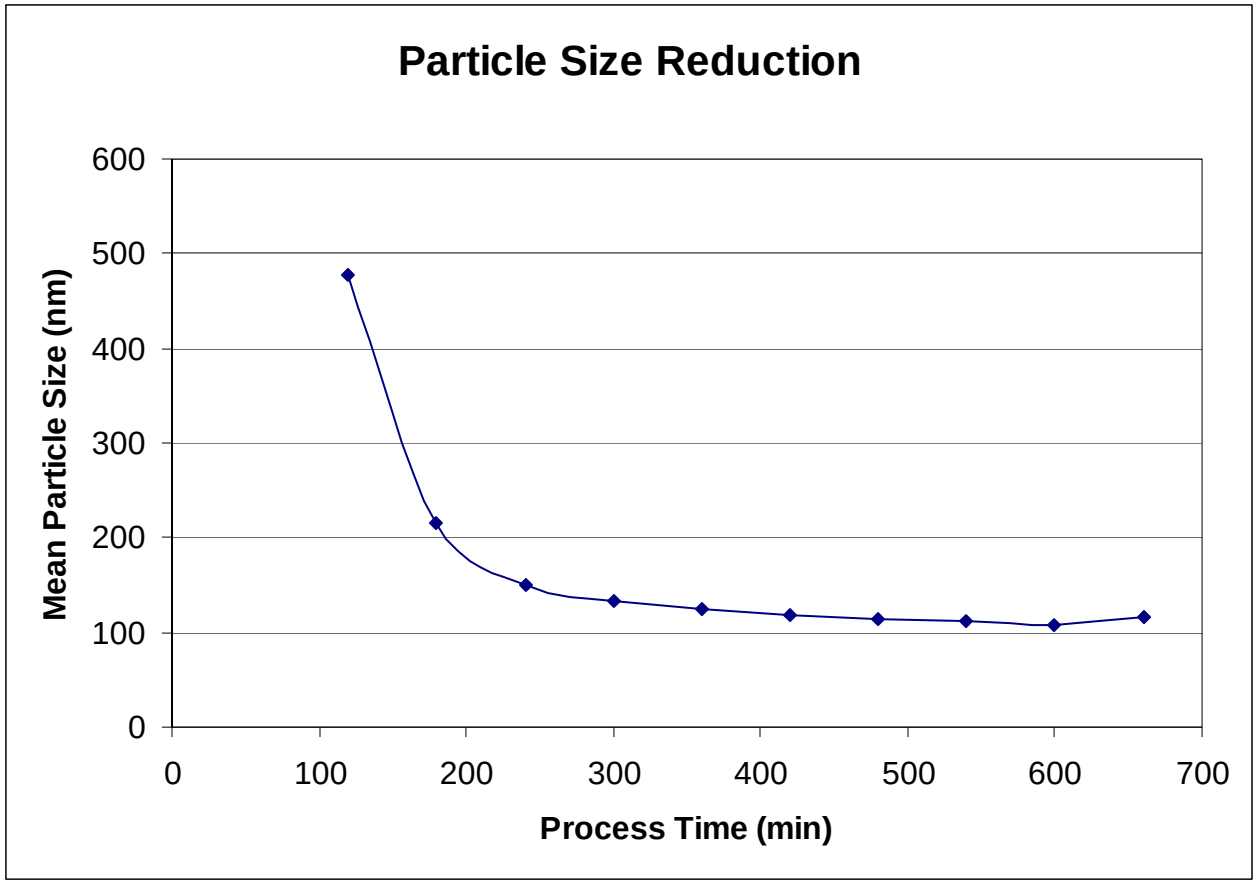
Characterization of Particle Size Distributions: Percentiles



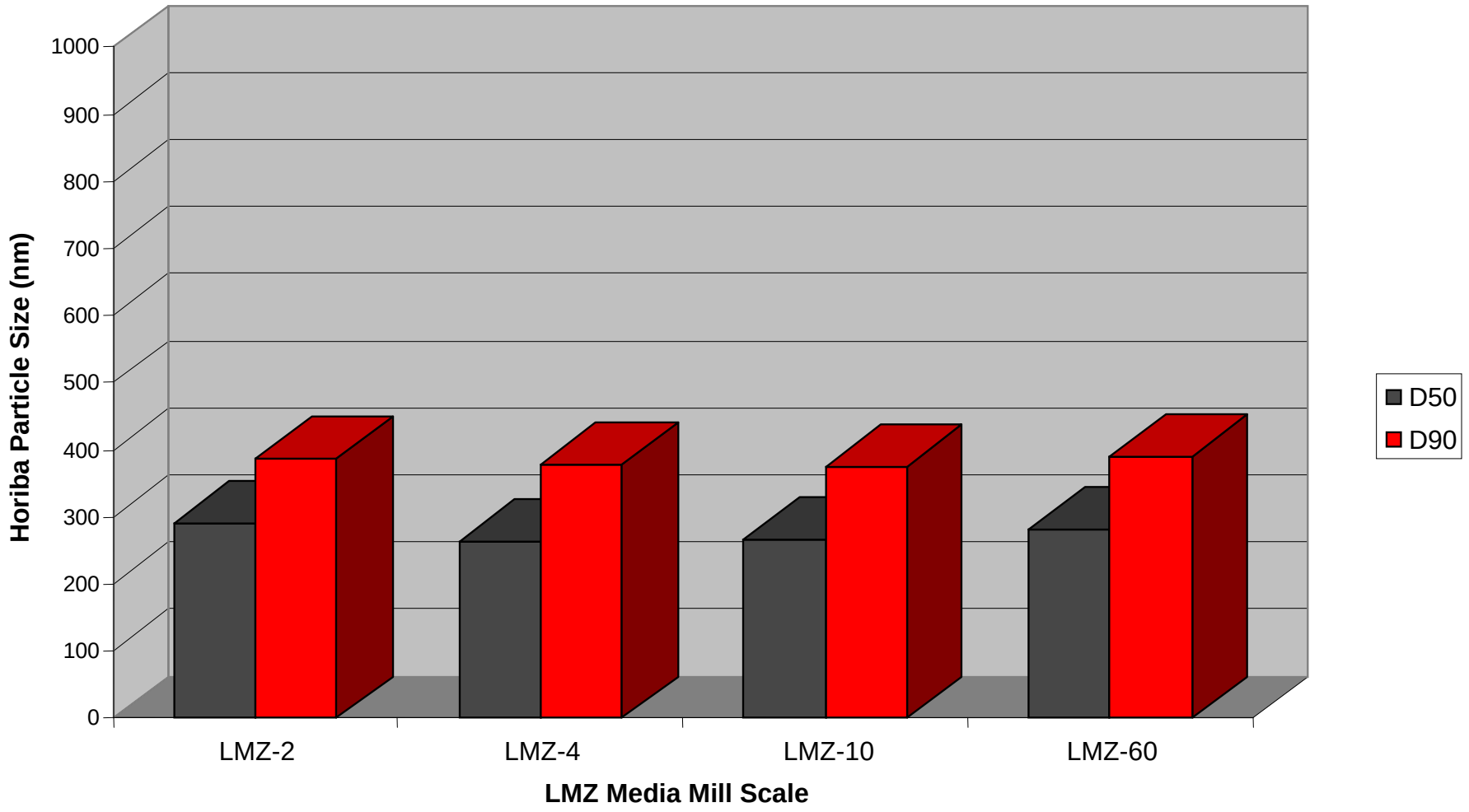
Change in Particle Size Distribution during Milling



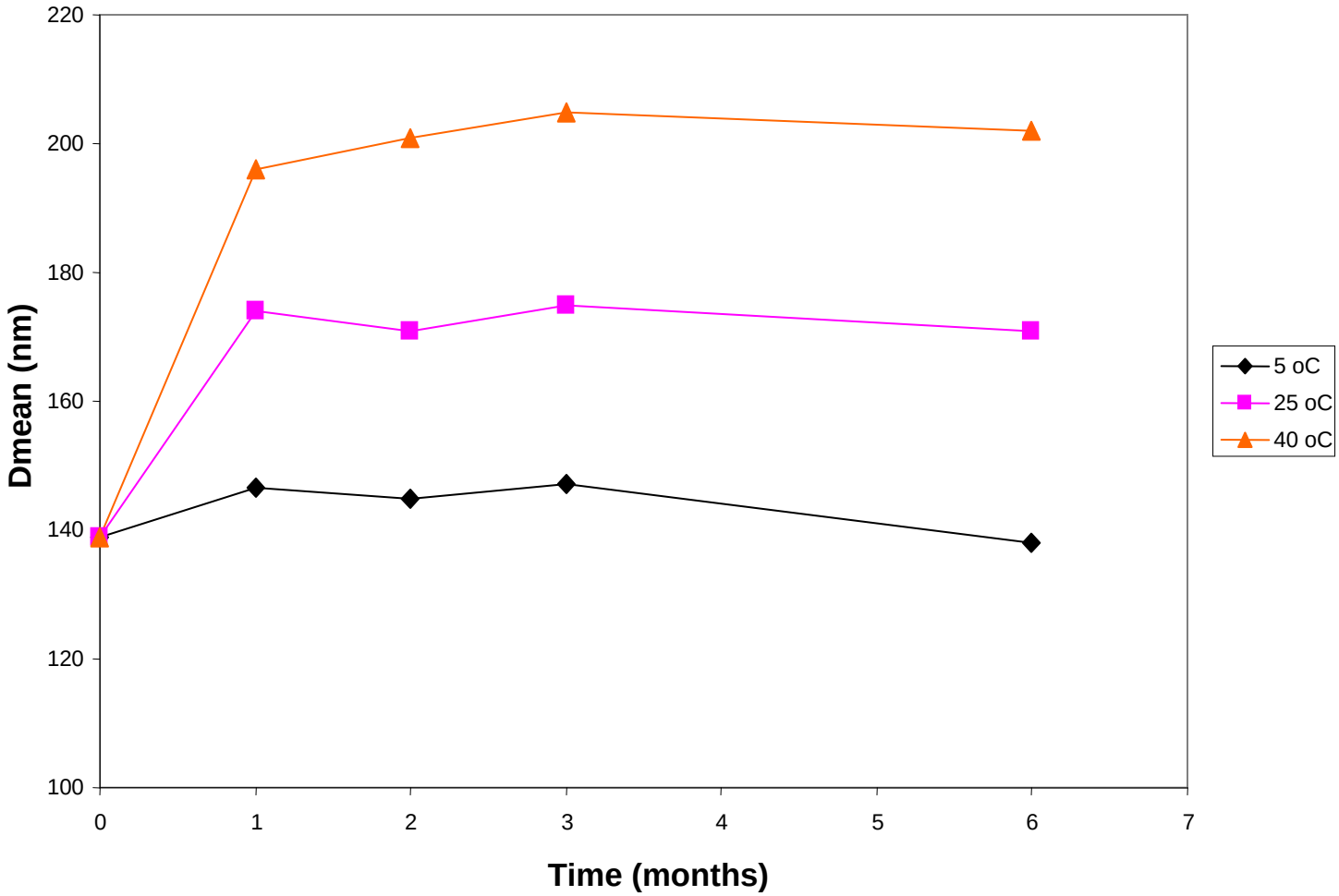
In-process particle sizing



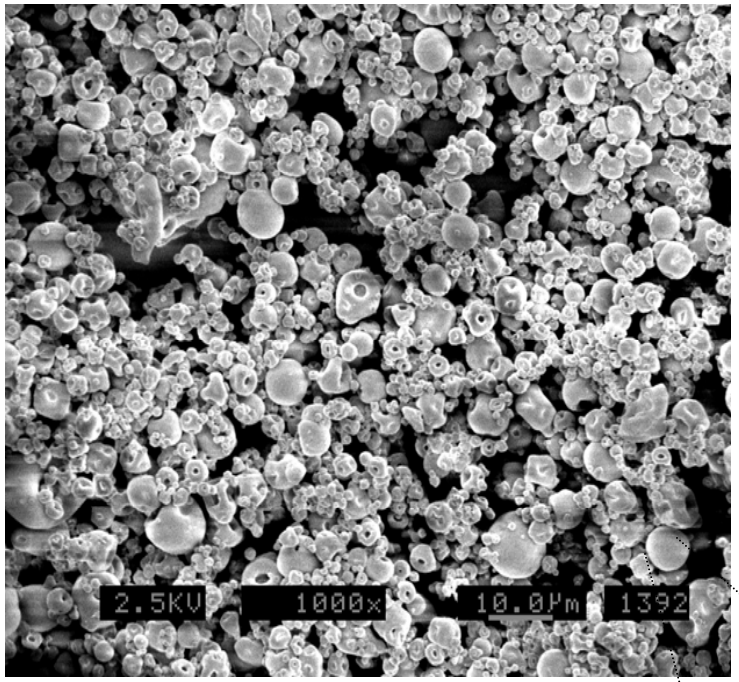
NanoCrystal Colloidal Dispersion® Formulation Scale-up

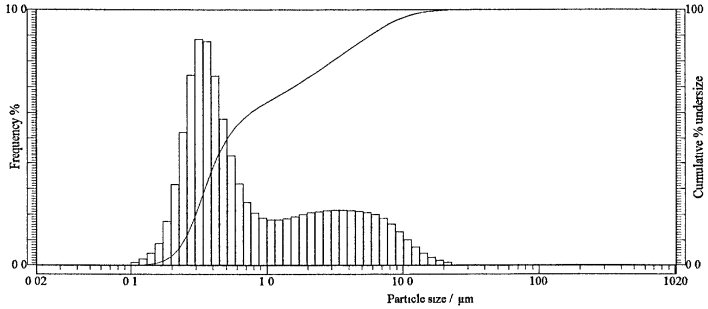


Monitoring Formulation Stability

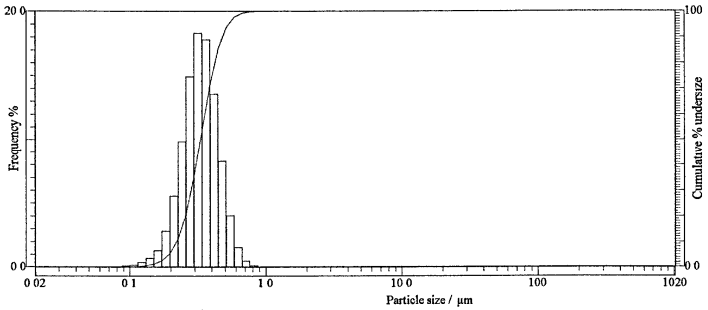


Redispersibility of Spray Processed NanoCrystal® Particles



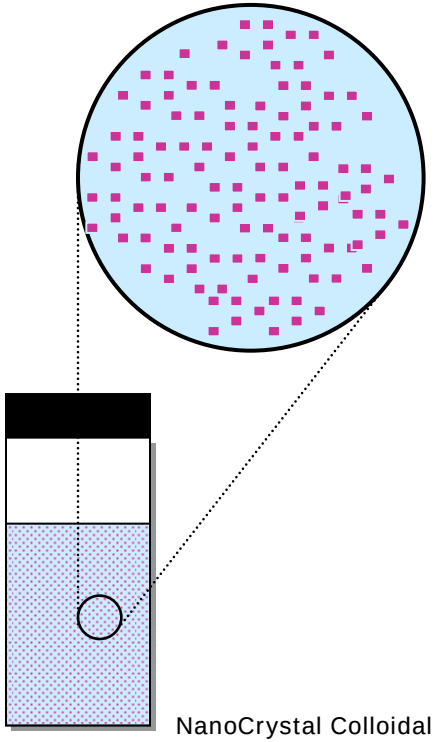


incomplete redispersibility

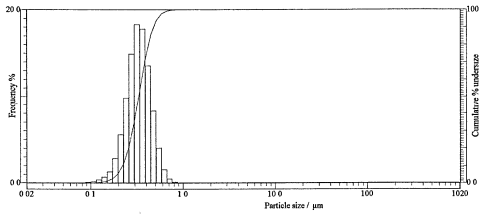


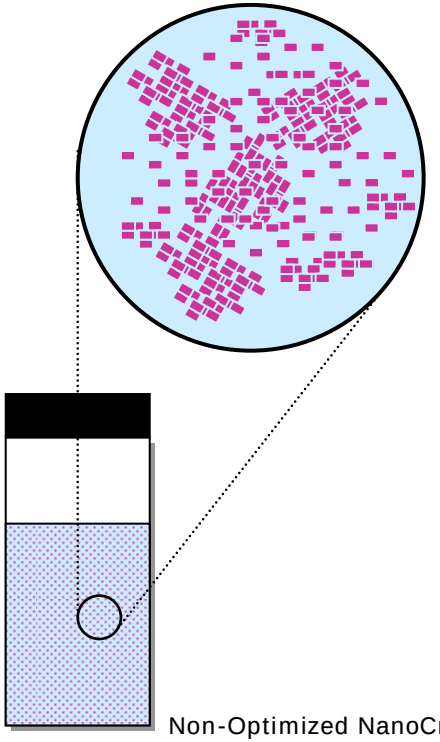
complete redispersibility

Redispersibility of Spray Processed NanoCrystal® Particles



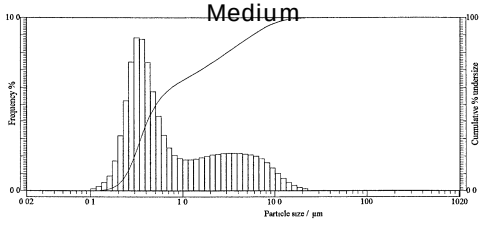
NanoCrystal Colloidal Dispersion composition in Redispersibility Medium

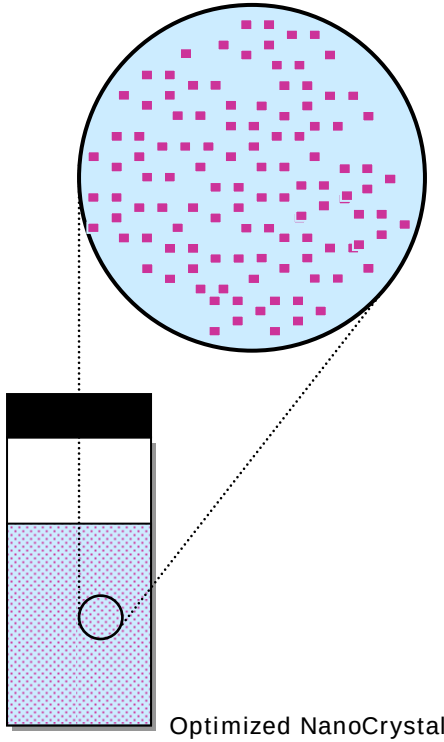




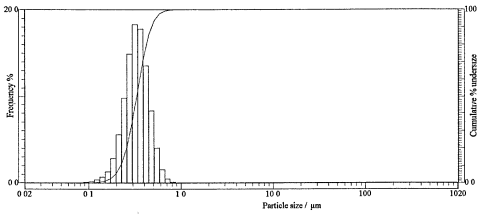
Non-Optimized NanoCrystal®

Solid composition in Redispersibility Medium





Optimized NanoCrystal Solid composition in Redispersibility Medium



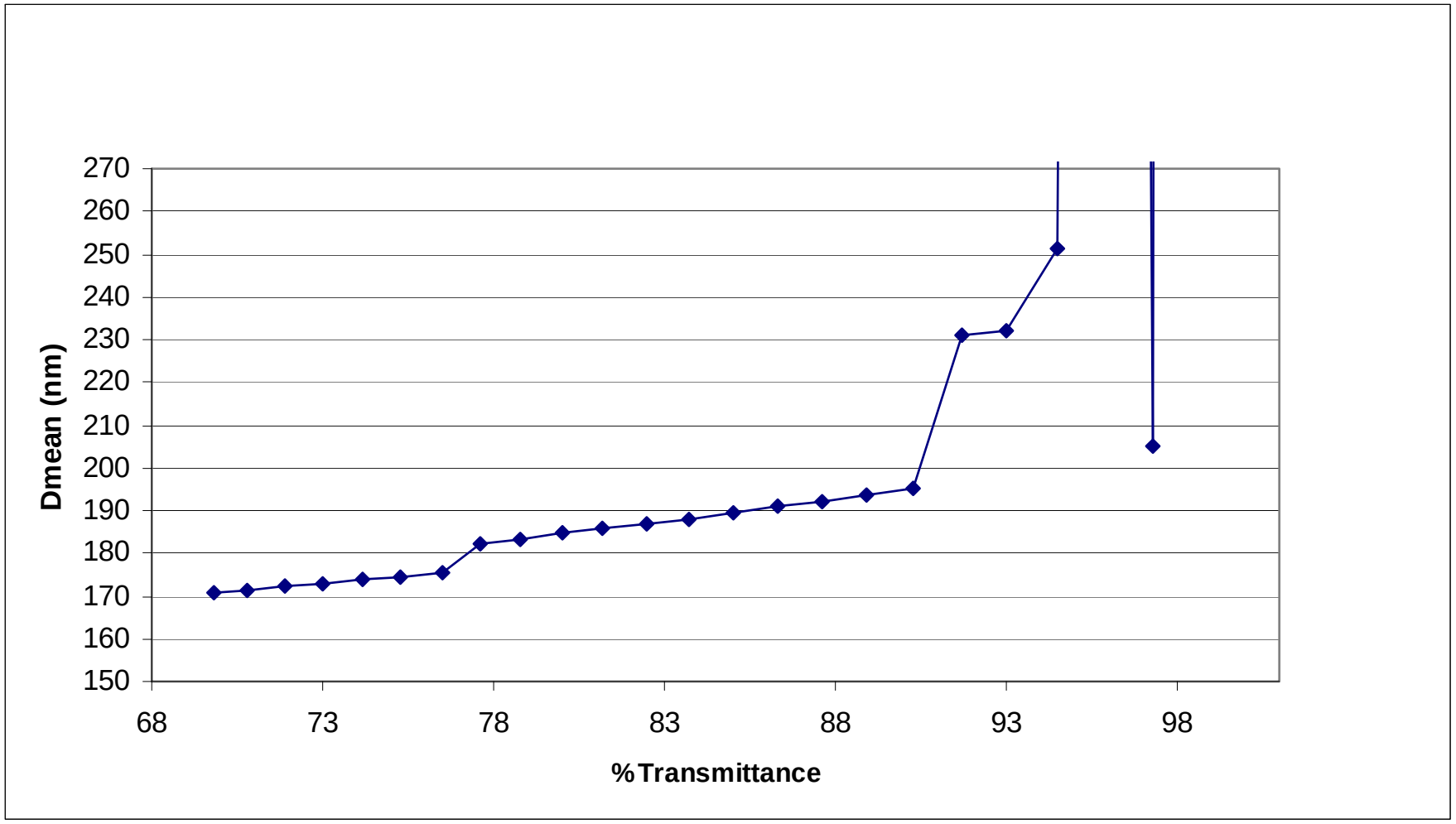
Particle sizing: Method Development

Dispersant

Concentration Optimization

Agitation/Circulation

Concentration Optimization



Instrumental Conditions

Exp #	Agitation	Circulation	$D_{mean\ (nm)}$	D_{10} (nm)	D_{90} (nm)
1	1	1	187.03	137.5	245.7
2	1	3	184.23	135.9	242.1
3	3	1	187.28	137.8	245.8
4	3	3	184.61	136.1	242.5
5	1	1	185.32	136.3	243.7
6	1	3	184.04	135.8	241.8
7	3	1	184.13	135.8	241.9
8	3	3	184.98	136.4	242.9
Parameters Selected: Agitation: 2 Circulation: 2					

Particle sizing: Method validation

Precision

- instrument
- inter-assay
- intermediate

Selectivity

Robustness

Particle Sizing: Precision

Design of Intermediate Precision Experiments				
1	N = 6 Assays	Day-1	Analyst-1	Instrument-1
2	N = 6 Assays	Day-1	Analyst-2	Instrument-1
3	N = 6 Assays	Day-1	Analyst-1	Instrument-2
4	N = 6 Assays	Day-1	Analyst-2	Instrument-2
5	N = 6 Assays	Day-2	Analyst-1	Instrument-1
6	N = 6 Assays	Day-2	Analyst-2	Instrument-1
7	N = 6 Assays	Day-2	Analyst-1	Instrument-2
8	N = 6 Assays	Day-2	Analyst-2	Instrument-2

Particle Sizing: Intermediate Precision LA910

				Grand RSD					
Analyst	Day	Instr.#	Replicate	Dmean (nm)	D5(nm)	D10(nm)	D50(nm)	D90(nm)	D95(nm)
1	1	1	1	107	45	56	95	171	211
1	1	1	2	107	45	56	95	171	210
1	1	1	3	106	45	56	94	168	206
1	1	1	4	107	45	56	95	170	209
1	1	1	5	106	45	55	94	169	208
1	1	1	6	103	45	55	93	163	195
1	1	2	1	102	44	53	88	165	200
1	1	2	2	101	44	53	87	163	206
1	1	2	3	101	44	53	87	162	202
1	1	2	4	100	44	53	87	161	201
1	1	2	5	101	44	53	87	161	202
1	1	2	6	98	44	53	87	152	188
1	2	1	1	108	45	56	96	172	212
1	2	1	2	108	45	56	96	171	210
1	2	1	3	106	45	56	95	168	205
1	2	1	4	107	45	56	95	169	208
1	2	1	5	107	45	56	95	169	208
1	2	1	6	106	45	56	95	168	206
1	2	2	1	103	44	53	89	166	211
1	2	2	2	103	44	53	88	167	210
1	2	2	3	102	44	53	89	165	207
1	2	2	4	102	44	53	88	164	206
1	2	2	5	102	44	53	88	164	206
1	2	2	6	101	44	53	88	163	205
2	1	1	1	107	45	55	94	172	214
2	1	1	2	107	45	55	94	173	216
2	1	1	3	105	45	55	93	168	207
2	1	1	4	106	45	55	93	170	212
2	1	1	5	106	45	55	93	171	213
2	1	1	6	106	45	55	93	169	208
2	1	2	1	102	44	53	88	164	209
2	1	2	2	100	44	53	87	161	202
2	1	2	3	100	44	53	87	158	198
2	1	2	4	100	44	53	86	158	199
2	1	2	5	100	44	53	87	159	200
2	1	2	6	99	44	53	87	157	197
2	2	1	1	109	45	56	97	176	216
2	2	1	2	108	45	56	96	174	214
2	2	1	3	107	45	56	95	170	208
2	2	1	4	106	45	55	94	169	208
2	2	1	5	106	45	55	94	170	209
2	2	1	6	106	45	56	94	169	207
2	2	2	1	103	44	54	89	165	209
2	2	2	2	104	44	53	89	169	217
2	2	2	3	103	44	53	88	167	212
2	2	2	4	102	44	53	88	165	210
2	2	2	5	101	44	54	88	162	203
2	2	2	6	101	44	54	89	161	200

	Grand RSD					
	Dmean (nm)	D5(nm)	D10(nm)	D50(nm)	D90(nm)	D95(nm)
Average	104	45	54	91	166	207
STDEV	3.0	0.5	1.3	3.5	5.0	5.8
% RSD	2.8	1.1	2.4	3.9	3.0	2.8
RSD limit	6%	10%	10%	6%	10%	10%

Instrument to instrument variability LA910: Formulation samples

Elan Drug Technologies

6-8 Instruments:

Formulation	Dmean	D10	D50	D90	Dmean	D10	D50	D90
	sd (nm)	sd (nm)	sd (nm)	sd (nm)	rsd (%)	rsd (%)	rsd (%)	rsd (%)
A	2.8	2.1	3.5	2.1	2.8	3.4	3.6	1.5
B	4.5	7.1	4.7	6.9	2.6	6.0	2.8	2.9
C	9.5	6.5	9.5	12.2	6.1	6.5	6.5	5.4
D	10.6	7.9	10.1	18.2	5.9	7.0	5.9	7.0
E	8.7	5.4	8.7	19.4	5.4	5.5	5.7	8.1
F	9.2	10.0	9.5	14.6	6.0	10.7	6.6	6.4

Particle Sizing: Precision (Repeatability) LA950

Elan Drug Technologies

Instrument 1:

Formulation 1	Dmean	D5	D10	D50	D90	D95
1	156	113	120	154	195	209
2	155	112	119	153	194	208
3	155	112	119	153	194	208
4	156	113	119	154	195	209
5	154	111	119	152	193	207
6	155	112	119	152	194	208
Average	155	112	119	153	194	208
Std Dev	0.8	0.8	0.5	1.0	0.8	0.7
RSD	0.5	0.7	0.4	0.6	0.4	0.4

Instrument 2:

Formulation 1	Dmean	D5	D10	D50	D90	D95
1	154	112	119	152	192	208
2	154	112	119	152	192	208
3	155	113	119	152	192	208
4	155	113	119	152	193	208
5	154	112	119	152	193	207
6	155	112	119	153	193	208
Average	155	112	119	152	192	208
Std Dev	0.5	0.5	0.0	0.6	0.3	0.5
RSD	0.3	0.5	0.0	0.4	0.1	0.3

Instrument to instrument variability LA950: Formulation samples

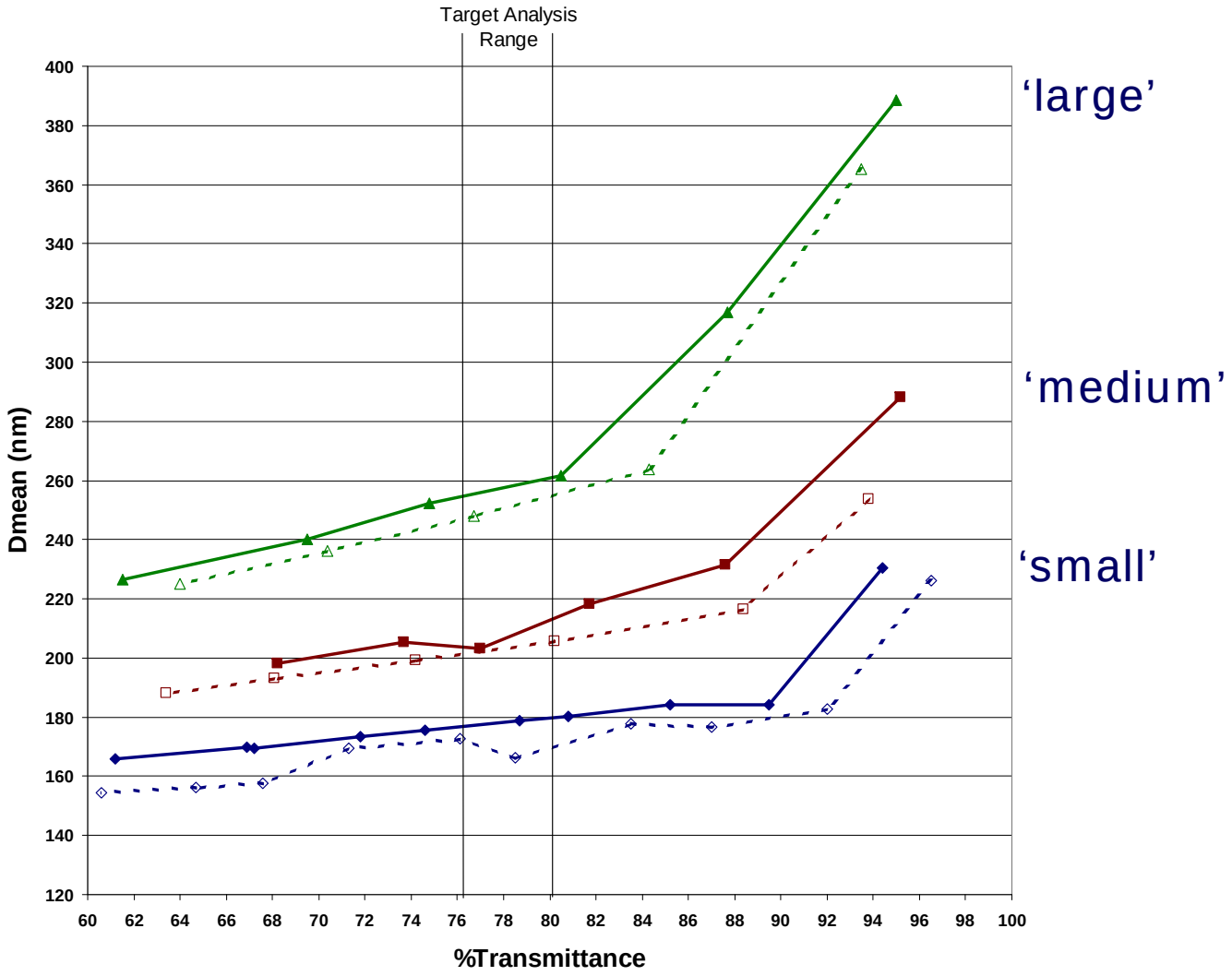
Elan Drug Technologies

4 Instruments:

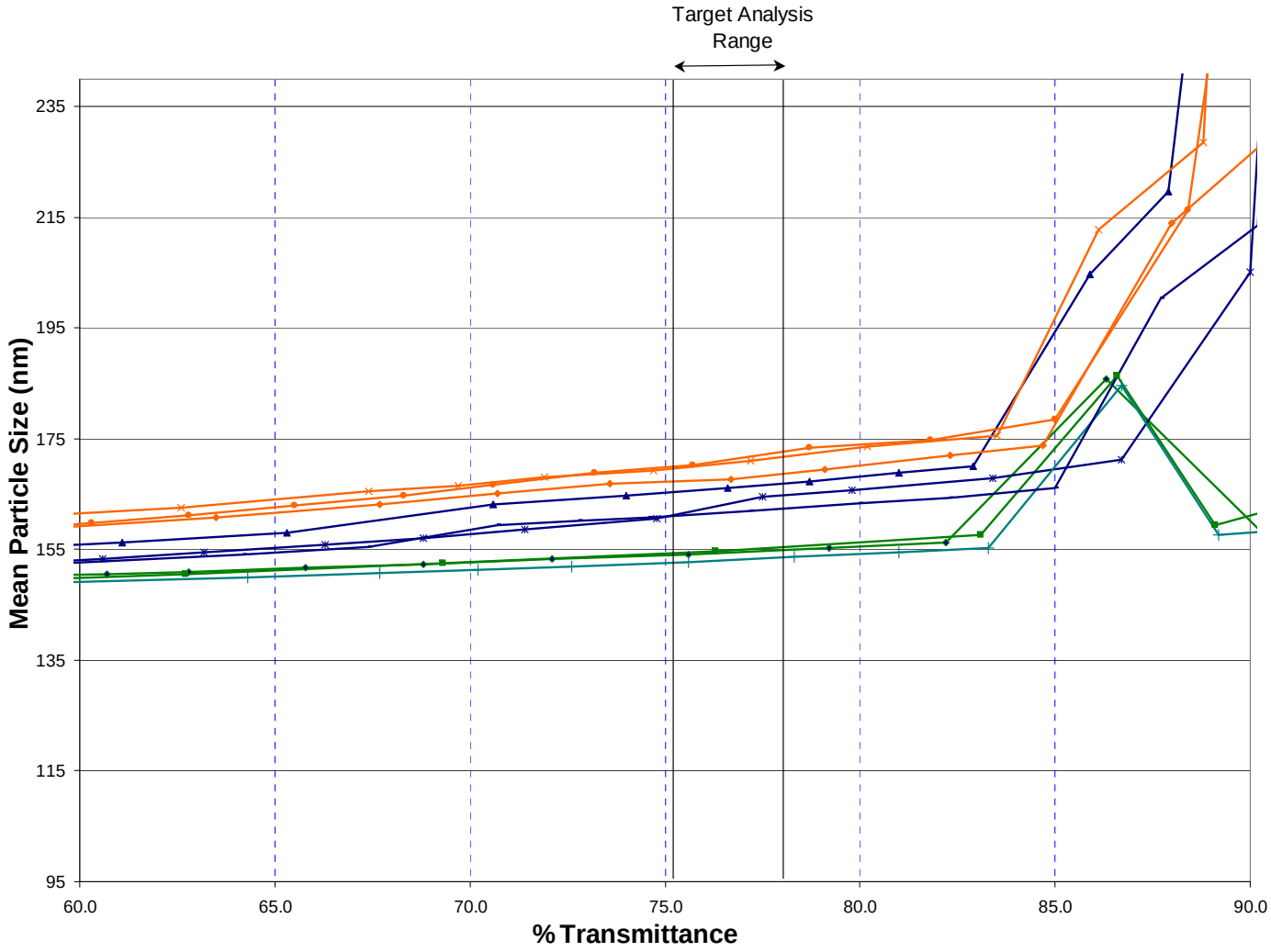
Formulation 1	Dmean	D5	D10	D50	D90	D95
Average (nm)	155	112	119	152	193	208
Std Dev (nm)	0.8	0.8	0.7	1.0	1.1	0.7
RSD (%)	0.5	0.7	0.6	0.6	0.6	0.3

Formulation 2	Dmean	D5	D10	D50	D90	D95
Average (nm)	193	136	147	187	247	264
Std Dev (nm)	1.5	0.5	0.4	0.6	0.4	1.1
RSD (%)	0.8	0.4	0.3	0.3	0.2	0.4

Selectivity LA950: Formulation 1



Selectivity LA950: Formulation 2



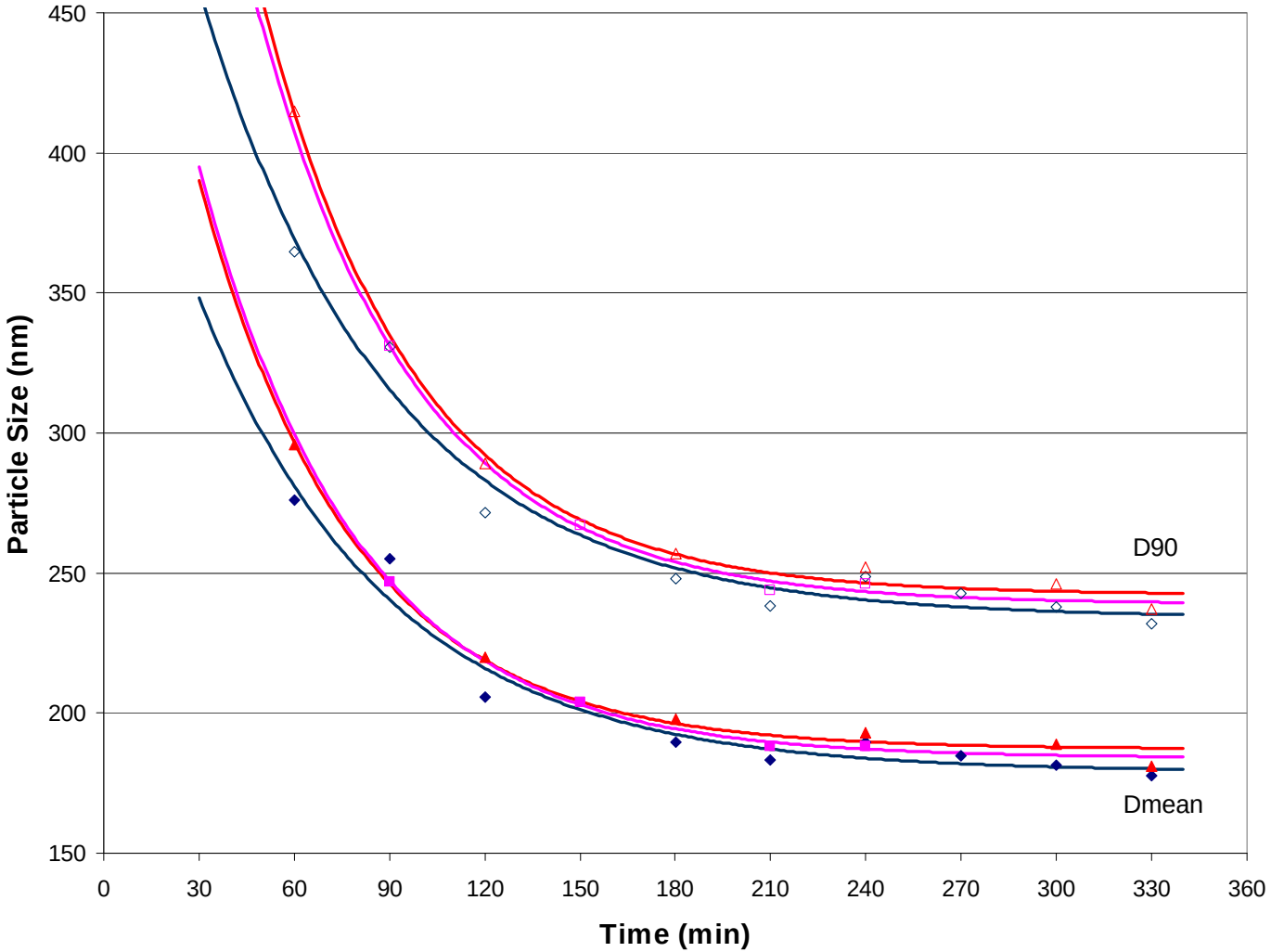
Robustness LA950 Method

		Parameter						
		A	B	C	D	E	F	G
Mean Particle Size (nm)	DOE Pattern	Agitation	Circulation	Waiting Time	Sampling Times	% Transmittance	Temperature of Dispersant	*
194	----+++	-1	-1	-1	-1	+1	+1	+1
185	--++--+	-1	-1	+1	+1	-1	-1	+1
185	-+-+-+-	-1	+1	-1	+1	-1	+1	-1
193	-++-+--	-1	+1	+1	-1	+1	-1	-1
194	+--++--	+1	-1	-1	+1	+1	-1	-1
187	+-+--+-	+1	-1	+1	-1	-1	+1	-1
184	++----+	+1	+1	-1	-1	-1	-1	+1
195	+++++++	+1	+1	+1	+1	+1	+1	+1

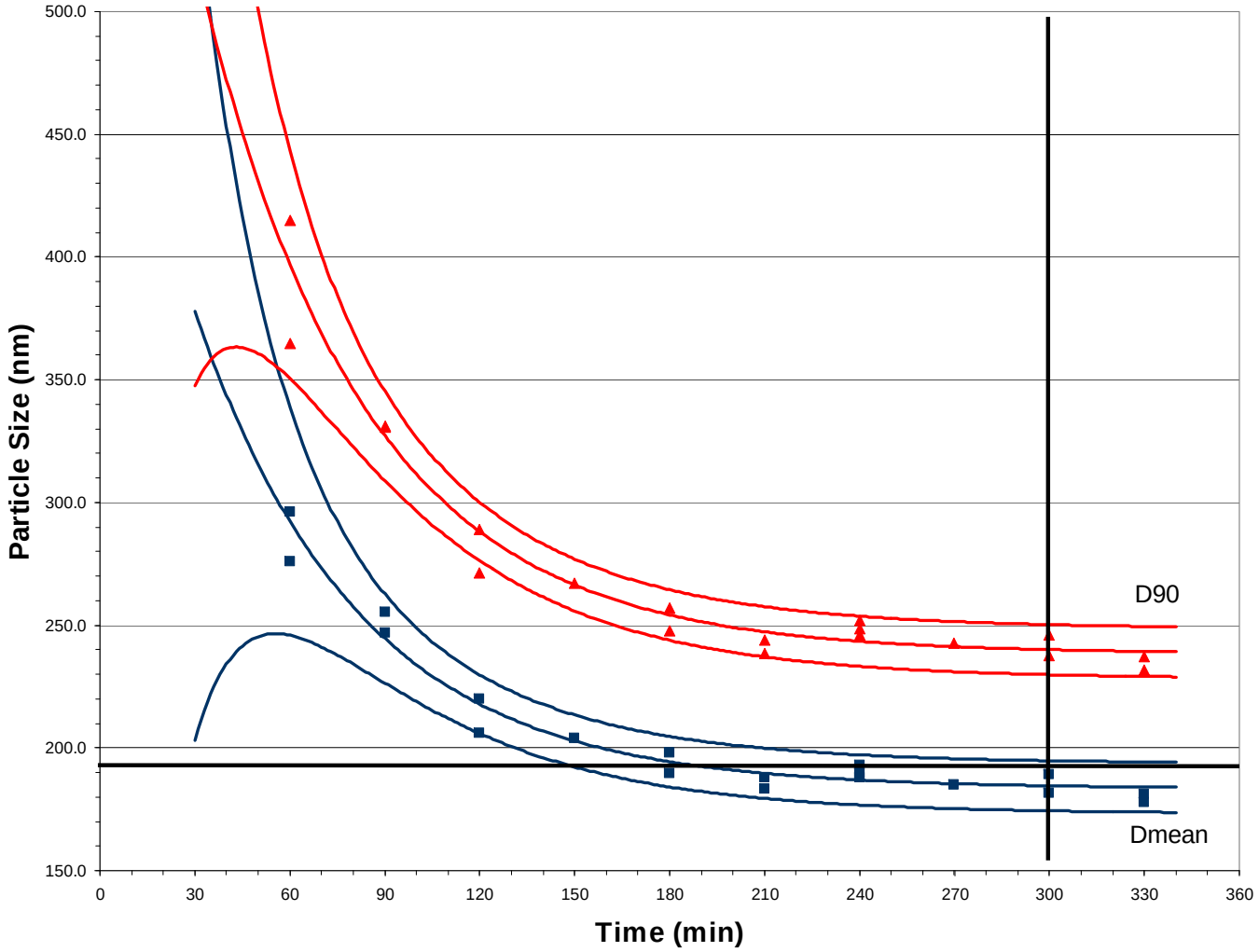
Robustness LA950 Method

Key	Agitation Level Setting	Circulation Level Setting	Waiting Time (Sec)	Sampling Times	% Transmittance	Temperature (°C)	*
Method Value	2	2	30	5000	83-87	Ambient	*
Max (+1) Value	3	3	40	6000	87-90	Ambient + 4°C	*
Min (-1) Value	1	1	20	4000	80-83	Ambient - 4°C	*
Particle Size Measurement Main Effect (D value)	1	-1	1	0	8	1	*
Standard Deviation (SD) of Main Effects	5						
SD x √2	7						
Main Effect Considered Significant [(P<0.05) if |D| > (SD x √2)] (Y/N)	No	No	No	No	Yes	No	*

In-Process Particle Sizing



In-Process Particle Sizing



Conclusion

Particle size analysis of NanoCrystal Colloidal Dispersion® Formulations by means of static laser light scattering is successfully used for:

- **Process control for manufacture**
- **Monitoring formulation stability**
- **Characterizing formulation performance**
- **Technology Transfer**

Crucial method characteristics:

- **Intermediate precision**
- **Robustness**

Elan Drug Technologies
The World's Leading Drug Delivery Company

WINNER
OF TECHNOLOGY
INNOVATION AWARD
at the 2010 Drug Delivery
Partnership Meeting

Top Drug Delivery Company of the Decade
-Drug Delivery Technology Survey, *May 2010*

For more information go to our website
www.elandrugtechnologies.com

For More Details

Visit www.horiba.com/us/particle

Contact HORIBA directly at labinfo@horiba.com

Visit the Download Center to find this recorded presentation and many more on other topics