Supplementary Materials

Do Mixtures of Beads with Different Sizes Improve Wet Stirred Media Milling of Drug Suspensions?

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S1. All supporting data and analysis (except the analysis performed by JMP software).

Table S1. Power per unit volume, apparent viscosity, and MHD parameters.

Run No.	P_w (W/m³)	μ_L (mPa.s)	g_0 (-)	θ (m²/s²)	u_b (m/s)	v (kHz)	σ_b^{max} (GPa)	α_b (μm)	a (mHz)	$\Pi\sigma_y$ (J²/m⁶s)
1	4.90×10^5	119	5.62	1.93×10^{-4}	2.22×10^{-2}	3.30	0.846	0.357	5.53	3.15×10^{15}
2	5.31×10^5	102	5.62	4.54×10^{-4}	3.40×10^{-2}	3.71	1.00	0.579	6.40	5.14×10^{15}
3	5.73×10^5	104	5.62	7.70×10^{-4}	4.43×10^{-2}	3.81	1.12	0.816	6.40	6.36×10^{15}
4	5.73×10^5	100	5.62	1.41×10^{-3}	5.99×10^{-2}	3.87	1.26	1.22	6.23	7.86×10^{15}
5	5.73×10^5	113	5.62	1.67×10^{-3}	6.52×10^{-2}	3.64	1.30	1.47	5.41	7.31×10^{15}
6	5.73×10^5	93	5.62	3.61×10^{-3}	9.58×10^{-2}	3.97	1.52	2.31	5.95	1.09×10^{16}
7	8.23×10^5	51.0	13.5	1.85×10^{-4}	2.17×10^{-2}	11.1	0.839	0.354	34.0	1.47×10^{16}
8	8.23×10^5	66.6	13.5	2.63×10^{-4}	2.59×10^{-2}	9.68	0.900	0.519	24.9	1.24×10^{16}
9	9.06×10^5	72.6	13.5	4.26×10^{-4}	3.29×10^{-2}	9.71	1.00	0.725	23.9	1.44×10^{16}
10	8.23×10^5	70.9	13.5	6.99×10^{-4}	4.22×10^{-2}	9.36	1.09	1.06	21.1	1.55×10^{16}
11	9.06×10^5	72.4	13.5	1.01×10^{-3}	5.08×10^{-2}	9.71	1.18	1.33	22.0	1.87×10^{16}
12	9.90×10^5	63.8	13.5	2.20×10^{-3}	7.48×10^{-2}	10.6	1.38	2.09	24.3	2.82×10^{16}
13	1.36×10^6	76.8	5.62	8.27×10^{-4}	4.59×10^{-2}	6.84	1.11	0.478	20.5	2.09×10^{16}
14	1.41×10^6	81.2	5.62	1.51×10^{-3}	6.19×10^{-2}	6.75	1.28	0.736	18.8	2.44×10^{16}
15	1.45×10^6	70.4	5.62	2.85×10^{-3}	8.52×10^{-2}	7.31	1.45	1.06	20.8	3.48×10^{16}
16	1.41×10^6	73.7	5.62	4.57×10^{-3}	0.108	6.98	1.59	1.55	18.0	3.64×10^{16}
17	1.49×10^6	82.1	5.62	5.84×10^{-3}	0.122	6.80	1.67	1.89	16.7	3.72×10^{16}
18	1.57×10^6	107	5.62	8.50×10^{-3}	0.147	6.09	1.80	2.74	12.9	3.34×10^{16}
19	1.78×10^6	27.1	13.5	7.47×10^{-4}	4.36×10^{-2}	22.3	1.11	0.468	119	8.97×10^{16}
20	1.78×10^6	40.5	13.5	9.40×10^{-4}	4.89×10^{-2}	18.3	1.16	0.670	78.4	6.48×10^{16}
21	1.91×10^6	30.9	13.5	2.03×10^{-3}	7.19×10^{-2}	21.1	1.36	0.991	97.5	1.10×10^{17}
22	1.91×10^6	52.0	13.5	2.16×10^{-3}	7.41×10^{-2}	16.4	1.37	1.33	58.3	6.72×10^{16}
23	1.91×10^6	47.7	13.5	3.08×10^{-3}	8.86×10^{-2}	16.9	1.47	1.66	59.8	7.94×10^{16}
24	1.99×10^6	59.0	13.5	4.66×10^{-3}	0.109	15.5	1.60	2.43	47.7	7.48×10^{16}
T1	7.40×10^5	68.8	8.37	2.49×10^{-4}	2.52×10^{-2}	6.86	0.890	0.376	17.8	9.84×10^{15}
T2	1.16×10^6	124	8.37	6.47×10^{-4}	4.06×10^{-2}	6.38	1.08	0.788	14.0	1.14×10^{16}
T3	1.20×10^6	94.9	8.37	3.65×10^{-3}	9.64×10^{-2}	7.30	1.52	2.31	15.4	2.50×10^{16}

Table S2. Inverse breakage rate constant, specific time and number of intermittent milling cycles for median particle size to reach 0.20 μm, power, Merit Scores, and capital cost of the beads used in each run.

Run No.	$1/k$ (min/ μm^{1-n})	t_{d50} (min)	N_{d50} (-)	N_{mc} (-)	P (kW)	Merit Score (-)[a]	Merit Score (-)[b]	Price ($)
1	3.43	25.2	1	1	0.047	74.4	64.6	92.3
2	5.24	37.7	1	1	0.050	61.7	48.5	72.4
3	4.67	40.8	1	1	0.053	63.7	44.5	52.5
4	8.60	39.7	1	1	0.053	44.5	45.5	59.6
5	4.04	36.2	1	1	0.053	67.5	49.0	39.7
6	4.76	38.0	1	1	0.053	63.2	47.2	26.9
7	0.65	12.4	1	6	0.073	80.9	71.5	132
8	0.68	11.4	1	8	0.073	80.7	73.0	103
9	0.72	11.6	1	7	0.080	77.0	69.7	75.0
10	0.85	11.7	1	10	0.073	79.4	72.6	85.1
11	0.78	12.1	1	12	0.080	76.6	68.9	56.7
12	1.17	14.3	1	11	0.087	70.8	63.1	38.5
13	0.82	17.4	3	28	0.117	48.5	39.1	92.3
14	0.86	19.7	5	38	0.120	38.0	29.3	72.4
15	1.75	16.5	5	46	0.123	34.3	30.7	52.5
16	1.96	18.3	5	49	0.120	34.3	30.2	59.6
17	1.24	15.2	5	48	0.127	35.2	30.9	39.7
18	2.01	22.5	8	61	0.133	22.6	18.2	26.9
19	0.20	4.62	2	56	0.150	46.3	46.3	132
20	0.21	5.71	3	75	0.150	41.4	40.5	103
21	0.33	7.12	3	77	0.160	38.4	36.9	75.0
22	0.41	6.23	3	75	0.160	38.1	37.6	85.1
23	0.53	6.83	3	78	0.160	37.7	37.1	56.7
24	0.65	9.65	6	106	0.167	25.7	24.1	38.5

[a]Merit score calculated via $1/k$, P, and N_{d50}. [b]Merit score calculated via t_{d50}, P, and N_{d50}.

Table S3. Root mean squared errors of the machine learning models based on MHD and process parameters.

Model	MHD parameters		Process parameters	
	Train[a]	Test	Train[a]	Test
Linear regression	0.346	0.241	0.553	0.493
Lasso regression	0.806	0.358	0.806	0.358
Ridge regression	0.332	0.213	0.523	0.491
Elastic net regression	0.440	0.180	0.518	0.465
Decision tree	0.400	0.526	0.474	0.116
Gradient boost	0.394	0.361	0.508	0.179
Random forest	0.414	0.308	0.489	0.198
k-nearest neighborhood	0.382	0.242	0.478	0.192

[a]RMSE of the leave-one-out cross validated predictions are reported.
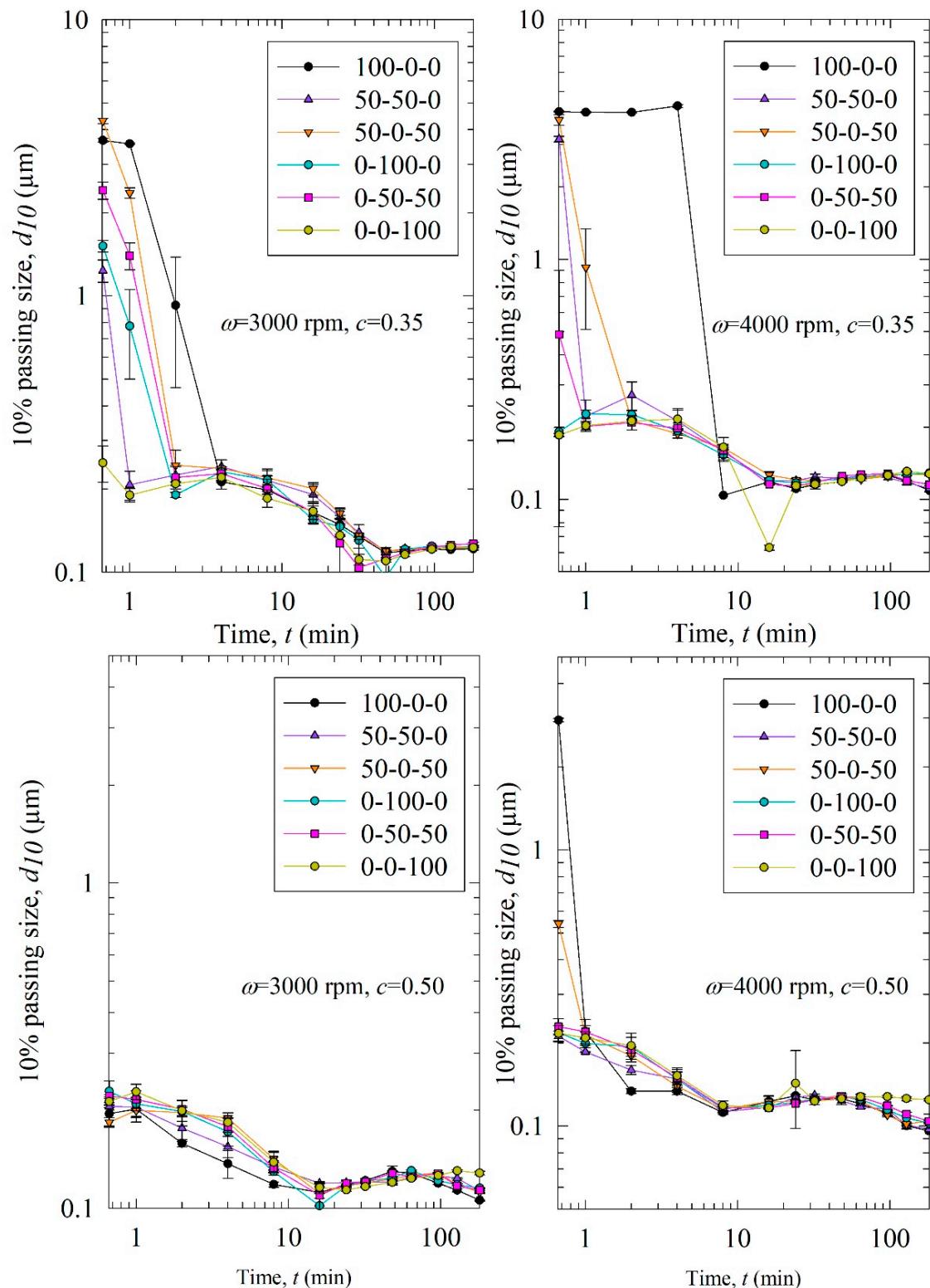
Figure S1. Timewise evolution of the 10% passing drug particle size d_{10} during 180 min of milling with various mass fractions of 100-200-400 μm beads at different stirrer speeds ω–bead loadings c.
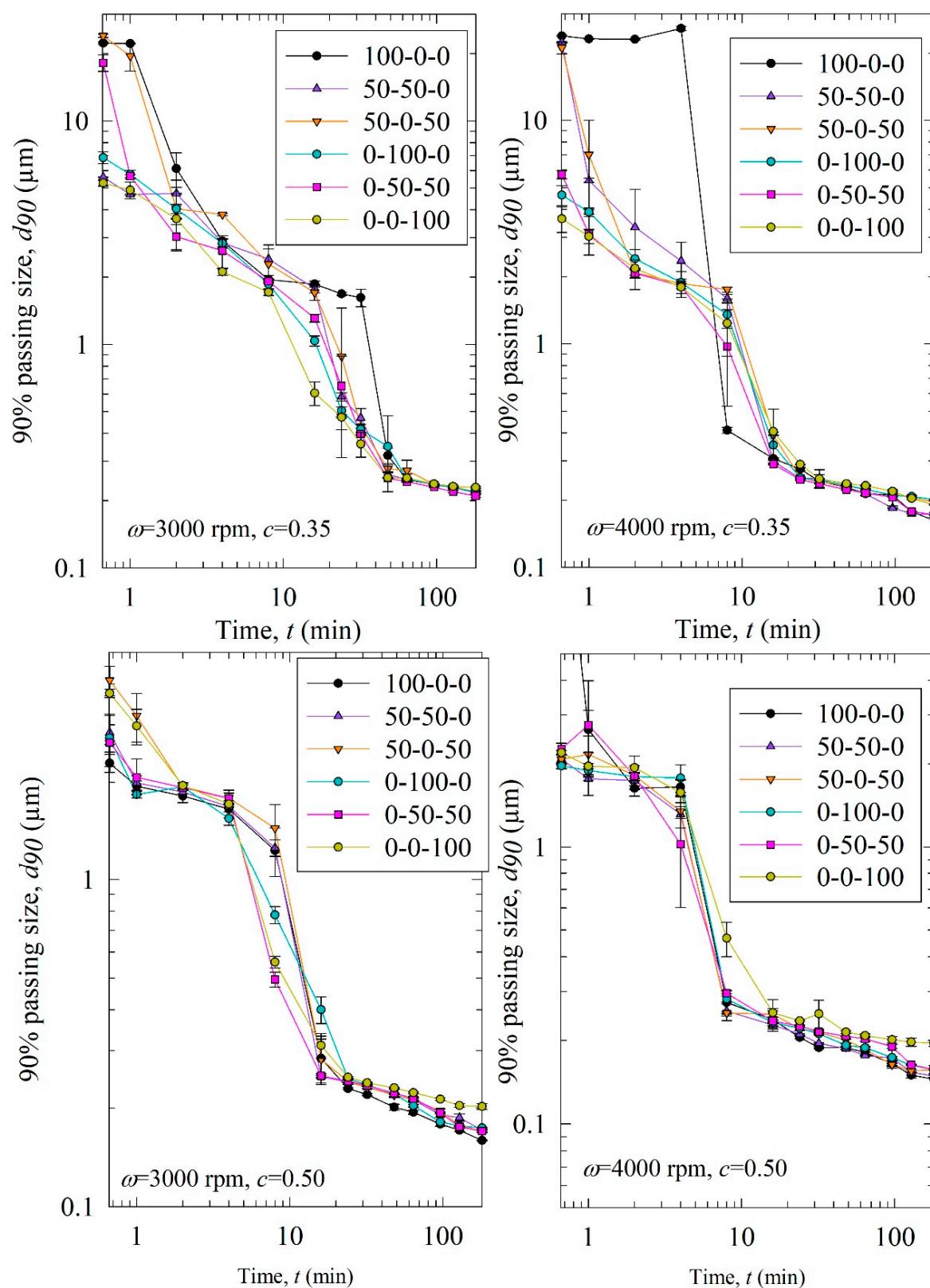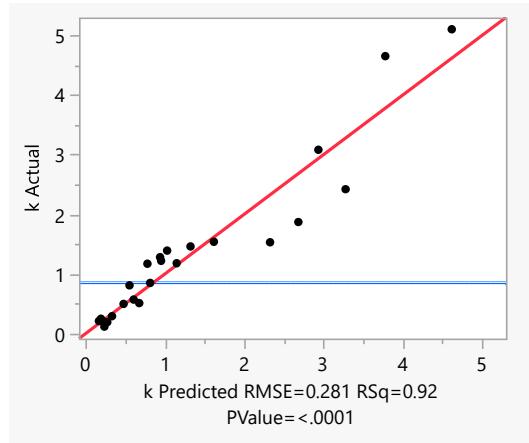
Figure S2. Timewise evolution of the 90% passing drug particle size d_{90} during 180 min of milling with various mass fractions of 100-200-400 μm beads at different stirrer speeds ω–bead loadings c.

S2. JMP regression report for the dependence of breakage rate constant k on stirrer speed (w), bead loading (c), and average bead size (D_b)

Whole Model Actual by Predicted Plot

Effect Summary

Source	Logworth		PValue
Log(BeadLoading)	159.616		0.00000
Log(RPM)	110.146		0.00000
Log(Db (mm))	37.115		0.00000

Summary of Fit

RSquare	0.923995
RSquare Adj	0.923308
Root Mean Square Error	0.28097
Mean of Response	-0.15459
Observations (or Sum Wgts)	336

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	3	318.62888	106.210	1345.379
Error	332	26.20942	0.079	**Prob > F**
C. Total	335	344.83830		<.0001*

Parameter Estimates
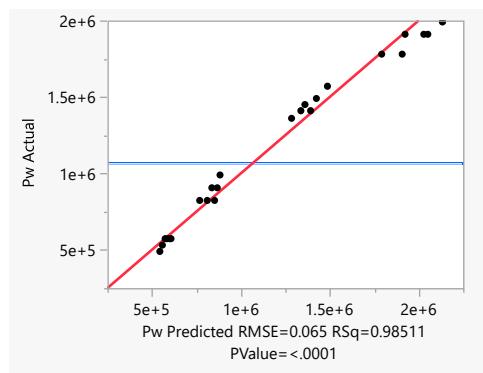
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-28.82373	0.870937	-33.10	<.0001*
Log(RPM)	3.6457431	0.106563	34.21	<.0001*
Log(BeadLoading)	4.4253755	0.08595	51.49	<.0001*
Log(Db (mm))	-0.49435	0.033738	-14.65	<.0001*

Note: * indicates statistically significance: p-value < 0.01 (orange color) and $0.01 \leqslant$ p-value < 0.05 (red color); * was not shown for lack of significance, i.e., p-value $\geqslant 0.05$ (black color in the probability column).

S3. JMP regression report for the dependence of average stirrer power per unit volume (P_w) on stirrer speed (w), bead loading (c), average bead size (D_b), and viscosity

Response Log(Pw)

Whole Model, Actual by Predicted Plot

Pw Predicted RMSE=0.065 RSq=0.98511
PValue=<.0001

Effect Summary

Source	LogWorth		PValue
Log(w)	14.223		0.00000
Log(c)	6.147		0.00000
Log(Db)	1.853		0.01403
Log(viscosity)	0.338		0.45912

Summary of Fit

RSquare	0.98511
RSquare Adj	0.981976
Root Mean Square Error	0.065042
Mean of Response	13.88355
Observations (or Sum Wgts)	24

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	4	5.3178261	1.32946	314.2611
Error	19	0.0803780	0.00423	**Prob > F**
C. Total	23	5.3982041		<.0001*

Parameter Estimates
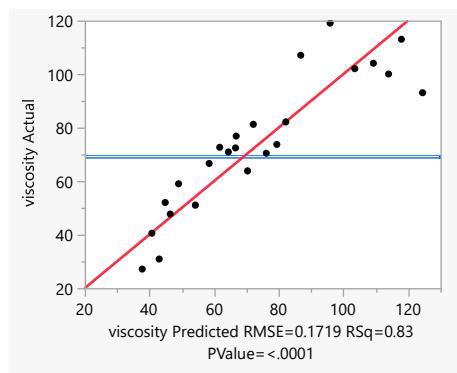
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-11.01764	1.278806	-8.62	<.0001*
Log(w)	3.0824606	0.140627	21.92	<.0001*
Log(c)	1.1182391	0.15444	7.24	<.0001*
Log(Db)	0.0900235	0.033277	2.71	0.0140*
Log(viscosity)	0.06392	0.084588	0.76	0.4591

Note: * indicates statistically significance: p-value < 0.01 (orange color) and $0.01 \leqslant$ p-value < 0.05 (red color); * was not shown for lack of significance, i.e., p-value $\geqslant$ 0.05 (black color in the probability column).

S4. JMP regression report for the dependence of viscosity of the nanosuspensions on the stirrer speed (*w*), bead loading (*c*), and average bead size (*D*b)

Response Log(viscosity)

Whole Model, Actual by Predicted Plot

Effect Summary

Source	LogWorth		PValue
Log(c)	7.041		0.00000
Log(w)	4.303		0.00005
Log(Db)	1.614		0.02432

Summary of Fit

RSquare	0.831127
RSquare Adj	0.805796
Root Mean Square Error	0.171936
Mean of Response	4.238615
Observations (or Sum Wgts)	24

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	3	2.9098542	0.969951	32.8108
Error	20	0.5912397	0.029562	**Prob > F**
C. Total	23	3.5010939		<.0001*

Parameter Estimates
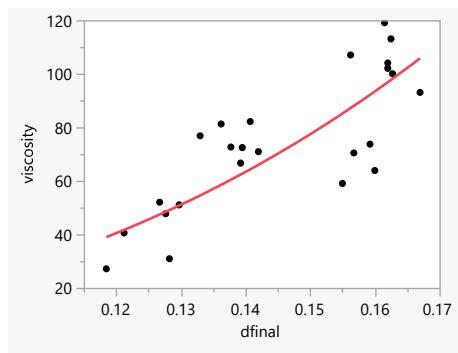
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	12.05937	2.0387	5.92	<.0001*
Log(w)	-1.254273	0.243994	-5.14	<.0001*
Log(c)	-1.599659	0.196797	-8.13	<.0001*
Log(Db)	0.1881845	0.077249	2.44	0.0243*

Note: * indicates statistically significance: p-value < 0.01 (orange color) and $0.01 \leqslant$ p-value < 0.05 (red color); * was not shown for lack of significance, i.e., p-value $\geqslant 0.05$ (black color in the probability column).

S5. JMP regression report for the dependence of viscosity of the nanosuspensions on their final median particle size (d_{f50})

Response Log(viscosity)

Whole Model, Regression Plot

Summary of Fit

RSquare	0.652295
RSquare Adj	0.63649
Root Mean Square Error	0.235232
Mean of Response	4.238615
Observations (or Sum Wgts)	24

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	2.2837446	2.28374	41.2720
Error	22	1.2173493	0.05533	**Prob > F**
C. Total	23	3.5010939		<.0001*

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	9.8707802	0.878008	11.24	<.0001*
Log(dfinal)	2.9107467	0.453082	6.42	<.0001*

Note: * indicates statistically significance: p-value < 0.01 (orange color) and $0.01 \leqslant$ p-value < 0.05 (red color); * was not shown for lack of significance, i.e., p-value $\geqslant$ 0.05 (black color in the probability column).