

SUPPLEMENT

Table S1. DoE models coefficients and terms*

Response	R ²	Q ²	Rep	Validity	Constant	T	SS	T*SS	p
Bulk density	0.875	0.336	0.872	0.582	0.588	-0.004	-0.024	-0.007	0.072
Tapped density	0.875	0.625	0.961	0.435	0.731	-0.006	-0.027	/	0.016
Flowability	0.987	0.462	0.970	0.840	8.886	-0.286	0.041	0.133	0.002
D 50 %	0.195	0.050	0.967	0.027	527.43	/	29.39	/	0.321
Residence time	0.945	0.383	0.966	0.422	42.286	0.204	-8.369	-0.167	0.022
Tensile strength	0.862	0.384	0.645	0.882	1.871	0.122	0	-0.167	0.083
Disintegration time	0.051	0.050	0.933	0.160	11.071	0.306	/	/	0.627
Dissolution	0.515	0.089	0.886	0.362	87.2	-2.613	-0.978	/	0.235

* R²: goodness of fit, Q²: predictive power, Rep: reproducibility, T*SS: interaction term between T and SS, and p: p-value of regression.

Table S2. Bulk and tapped density (mg/mL) of PM and granules after calibration (n=3).

		Number of taps				
Batch		0	10	110	1110	3110
Av	PM	521.4	540.4	688.7	751.6	765.2
	185/60	613.1	665.5	705.1	751.6	763.2
	185/100	577.3	614.4	641.0	687.3	711.9
	225/60	616.9	664.0	710.2	742.2	763.3
	225/100	547.4	583.0	619.5	661.0	685.5
	205/80/1	569.9	613.4	655.5	695.2	715.5
	205/80/2	580.9	615.9	656.8	698.5	717.1
	205/80/3	563.0	599.5	641.0	685.6	710.2
SD	PM	2.6	5.6	4.6	5.4	4.8
	185/60	3.1	5.6	0.0	2.7	2.8
	185/100	2.8	3.6	5.8	11.1	4.8
	225/60	0.0	4.2	7.2	4.6	5.6
	225/100	2.9	3.3	3.7	4.2	3.9
	205/80/1	15.2	14.4	15.0	8.0	11.3
	205/80/2	11.2	11.0	12.5	9.2	8.8
	205/80/3	6.0	3.4	5.8	10.2	7.2

Table S3. Flowability (g/s) of physical mixture (PM) and granulated samples after calibration (n=3).

Sample	# 1	# 2	# 3	Av.	SD
PM	-	-	-	-	-
185/60	9.2	9.4	9.6	9.4	0.18
185/100	9.3	9.1	9.0	9.1	0.14
225/60	8.1	8.3	8.4	8.3	0.12
225/100	8.9	8.8	8.8	8.8	0.07
205/80/1	8.8	8.7	8.8	8.8	0.06
205/80/2	8.9	8.8	8.8	8.9	0.04
205/80/3	8.9	8.8	8.9	8.9	0.07

Table S4. Angle of Repose (°) of PM and granulated samples after calibration (n=3).

Sample	# 1	# 2	# 3	Av.	SD
PM	-	-	-	-	-
185/60	41.5	44.4	43.6	43.2	1.22
185/100	41.5	41.4	40.4	41.1	0.50
225/60	43.7	48.2	46.6	46.2	1.86
225/100	43.8	41.4	42	42.4	1.02
205/80/1	44.5	43.3	43.9	43.9	0.49
205/80/2	41.7	42	42.9	42.2	0.51
205/80/3	41.6	42.9	44.5	43.0	1.19

Table S5. Tablet tensile strength (TS; Av.±SD, n=10) and mass loss after friability test (n=1).

Sample	TS, MPa	Before, g	After, g	Mass loss, %
185/60	1.49±0.3	1.342	1.339	0.224
185/100	1.96±0.2	1.405	1.402	0.214
225/60	2.32±0.0	1.461	1.458	0.205
225/100	1.75±0.2	1.318	1.315	0.228
205/80/1	2.05±0.3	1.440	1.437	0.208
205/80/2	1.77±0.2	1.356	1.353	0.221
205/80/3	1.67±0.2	1.385	1.382	0.217

Table S6. Reported disintegration time (s) of tablets (n=6).

Formulation	#1	#2	#3	#4	#5	#6	Av.	S.D.	R.S.D.
185/60	639	646	654	712	722	753	687.7	43.35	6.30
185/100	636	681	694	708	722	764	700.8	39.01	5.57
205/80/1	540	558	570	652	672	679	611.8	57.09	9.33
205/80/2	537	545	554	612	626	687	593.5	53.61	9.03
205/80/3	516	523	574	579	590	637	569.8	41.05	7.20
225/60	772	793	800	817	836	841	809.8	24.22	2.99
225/100	632	668	674	680	694	700	674.7	22.02	3.26

Table S7. Drug released (% of dose) in a dissolution test.

	Time pint, min	185/60	185/100	205/80 (1)	205/80 (2)	205/80 (3)	225/60	225/100
Av.	3	15.7	16.1	14.9	15.7	15.2	15.3	16.5
	6	24.9	25.1	23.8	25.8	24.2	23.5	24.7
	9	34.3	34.0	33.6	35.7	34.4	31.3	32.9
	12	43.8	42.6	42.9	45.4	43.6	38.3	40.5
	15	53.2	51.3	51.9	54.5	52.8	46.8	48.9
	18	62.7	59.0	60.9	63.2	61.4	54.3	56.4
	21	70.8	66.5	68.3	70.7	69.8	61.7	63.9
	24	78.2	73.7	75.8	78.6	76.7	68.9	70.7
	27	85.0	79.7	82.7	85.6	83.6	75.0	76.4
	30	91.4	85.8	88.4	91.0	89.4	81.8	82.6
	33	96.5	90.6	93.0	95.6	94.4	87.2	87.3
	36	98.3	94.6	96.8	98.5	97.1	91.9	91.7
	39	99.1	97.5	98.8	99.9	98.9	95.5	95.5
	42	99.4	99.0	99.7	100.0	99.8	98.1	97.7
	45	99.4	99.6	100.0	100.0	100.0	99.4	99.1
	48	99.4	99.8	100.0	100.0	100.0	99.9	99.7
	51	99.4	99.9	100.0	100.0	100.0	100.0	99.9
	54	99.5	100.0	100.0	100.0	100.0	100.0	100.0
	57	99.6	100.0	100.0	100.0	100.0	100.0	100.0
	60	100.0	100.0	100.0	100.0	100.0	100.0	100.0
SD	3	0.5	0.6	0.4	0.8	0.4	0.3	1.1
	6	0.9	0.8	1.0	1.9	0.9	1.8	1.3
	9	0.5	1.1	2.0	1.5	1.3	2.2	2.0
	12	1.2	0.9	2.5	1.5	2.3	2.6	1.3
	15	2.2	0.7	3.2	1.4	2.7	3.1	1.2
	18	2.0	0.8	3.9	1.4	3.6	3.0	1.0
	21	2.6	1.5	3.2	1.6	3.4	3.5	1.0
	24	3.4	1.4	3.4	1.0	4.3	3.6	0.5
	27	3.4	1.8	4.0	1.8	4.4	3.4	0.5
	30	3.4	1.2	3.6	0.8	4.4	3.5	0.3
	33	2.2	1.1	2.9	0.7	3.8	3.5	0.3
	36	1.2	1.2	1.8	0.3	2.1	3.0	0.5
	39	0.7	0.9	0.9	0.1	0.8	2.5	0.3
	42	0.8	0.7	0.4	0.0	0.2	1.6	0.2
	45	0.8	0.3	0.0	0.0	0.0	0.5	0.1
	48	0.8	0.1	0.0	0.0	0.0	0.1	0.0
	51	0.8	0.0	0.0	0.0	0.0	0.0	0.0
	54	0.7	0.0	0.0	0.0	0.0	0.0	0.0
	57	0.6	0.0	0.0	0.0	0.0	0.0	0.0
	60	0.0	0.0	0.0	0.0	0.0	0.0	0.0

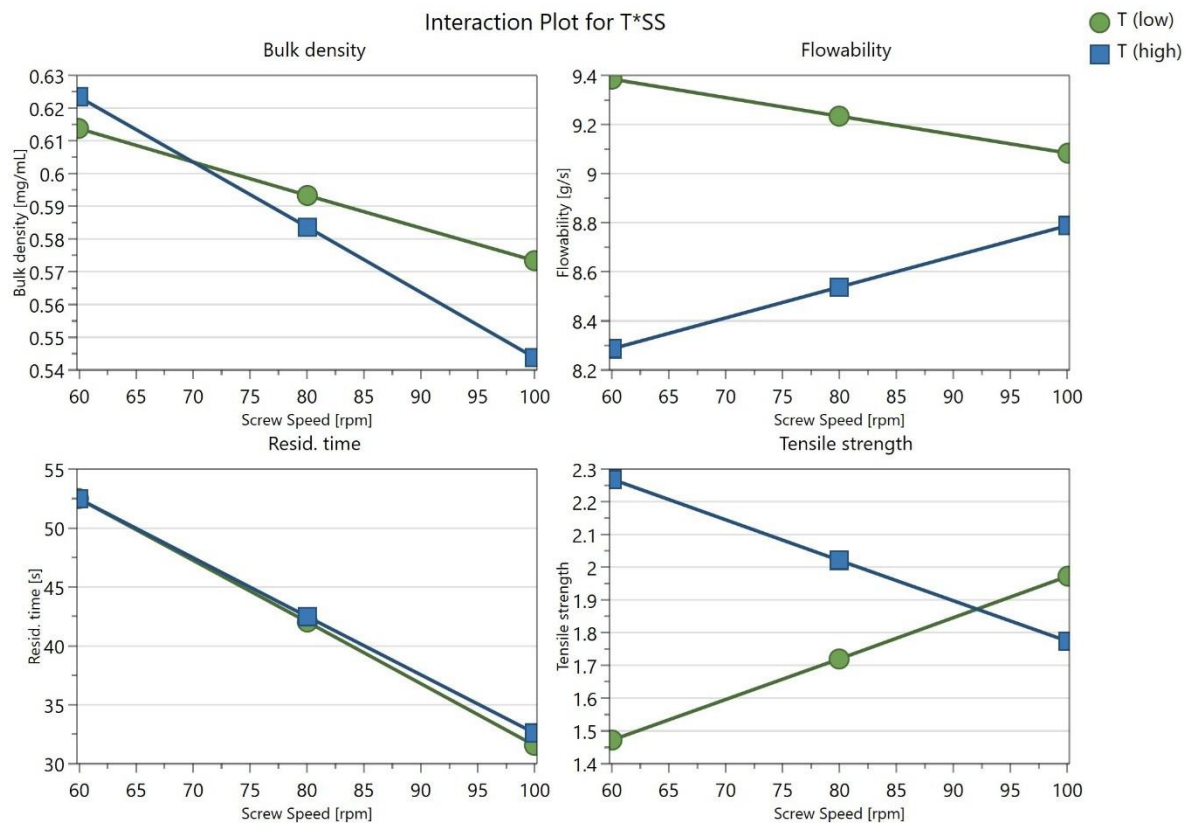


Fig. S1. Interaction term ($T \cdot SS$) for the responses (bulk density, flowability, residence time and tensile strength) that showed complex interaction between process conditions (as shown in Table S1).

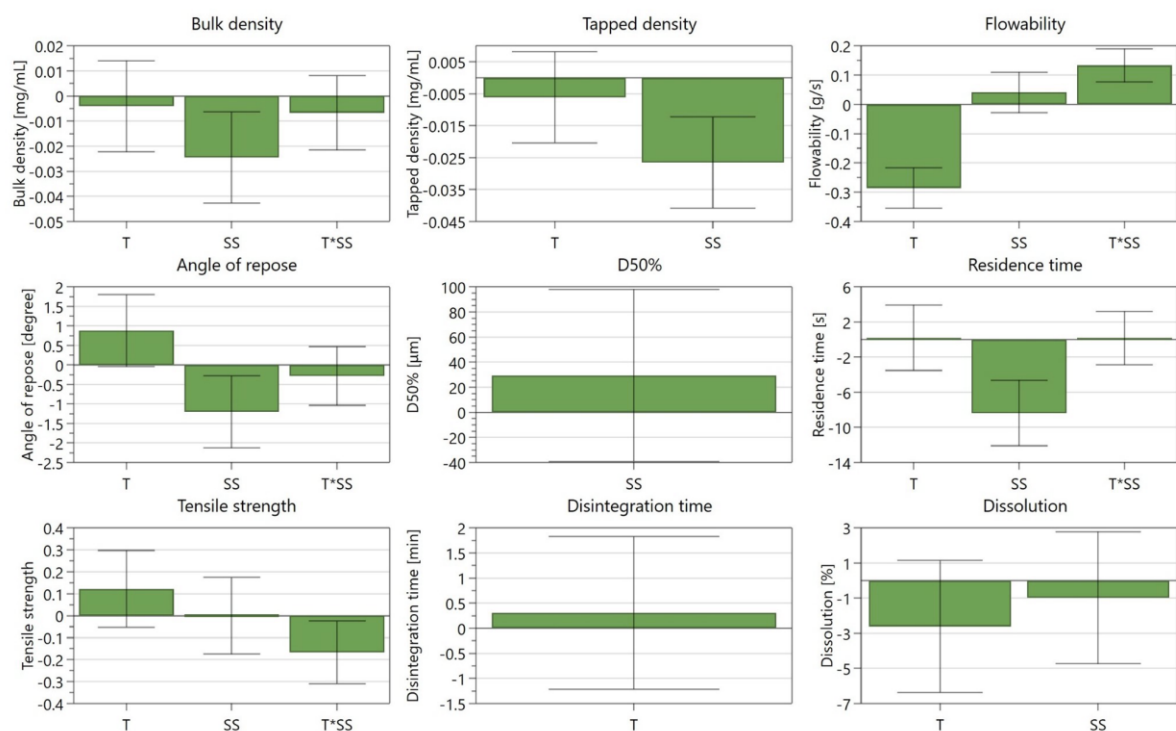


Fig. S2. Coefficient plots showing regression coefficients (green bars) with confidence intervals (error bars) of the variables for each response.