

Table S1. Polynomial equations of DoE.

Curcumin	
T. Plate = 7997.63 – 900.09 x (Flow) + 2230.77 x (MP Composition) – 216.27 x (Flow) x (MP Composition) – 27.11 x (Flow) ² + 332.44 x (MP Composition) ²	
Retention Time = 5.92284 – 2.47917 x (Flow) + 2.50043 x (MP Composition) – 0.92945 x (Flow) x (MP Composition) + 0.83732 x (Flow) ² + 0.85824 x (MP Composition) ²	
Atorvastatin calcium	
T. Plate = 10122.34 – 789.65 x (Flow) + 2579.54 x (MP Composition) + 200.40 x (Flow) x (MP Composition) - 833.98 x (Flow) ² – 190.50 x (MP Composition) ²	
Retention Time = 6.87806 - 2.33727 x (Flow) + 2.91718 x (MP Composition) – 0.54295 x (Flow) x (MP Composition) + 0.50954 x (Flow) ² + 0.78381 x (MP Composition) ²	
Resolution = 2.56646 + 0.03749 x (Flow) + 1.83279 x (MP Composition) – 0.06094 x (Flow) x (MP Composition) + 0.09613 x (Flow) ² + 0.26467 x (MP Composition) ²	
Celecoxib	
T. Plate = 13802.36 – 716.66 x (Flow) + 2083.86 x (MP Composition) + 530.05 x (Flow) x (MP Composition) – 400.60 x (Flow) ² – 750.78 x (MP Composition) ²	
Retention Time = 10.90207 – 2.80362 x (Flow) + 3.79246 x (MP Composition) + 0.23224 x (Flow) x (MP Composition) - 0.03713 x (Flow) ² + 0.33921 x (MP Composition) ²	

Table S2. ANOVA and t-test parameters for the characterization of the DoE responses.

Curcumin						
T.plate	β₀	β₁	β₂	β₁₂	β₁₁	β₂₂
t value p value	71.252 < 2e-16 ***	-14.641 < 2e-16 ***	36.285 < 2e-16 ***	-2.872 0.00449 **	-0.255 0.79927	3.122 0.00205 **
Degrees of freedom Sum of squares Mean square F significance p value		1 116663768 116663768 212.0145 < 2.2e-16 ***	1 716595369 716595369 1302.2777 < 2.2e-16 ***	1 4490116 4490116 8.1599 0.004719 **	1 35283 35283 0.0641 0.800348	1 5304795 5304795 9.6405 0.002170 **
Retention Time	β₀	β₁	β₂	β₁₂	β₁₁	β₂₂
t value p value	220.43 < 2e-16 ***	-168.45 < 2e-16 ***	169.90 < 2e-16 ***	-51.56 < 2e-16 ***	32.85 < 2e-16 ***	33.67 < 2e-16 ***
Degrees of freedom Sum of squares Mean square		1 885.06 885.06	1 900.31 900.31	1 82.93 82.93	1 33.65 33.65	1 35.36 35.36

F significance p value		813593 < 2.2e-16 ***	827610 < 2.2e-16 ***	76235 < 2.2e-16 ***	30935 < 2.2e-16 ***	32500 < 2.2e-16 ***
Tailing Factor	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	138.523 <2e-16 ***	0.180 0.857	-9.614 <2e-16 ***	-0.579 0.563	0.225 0.822	-0.269 0.788
Degrees of freedom Sum of squares Mean square F significance p value		1 0.00014 0.00014 0.0321 0.8580	1 0.39250 0.39250 91.2871 <2e-16 ***	1 0.00143 0.00143 0.3317 0.5653	1 0.00022 0.00022 0.0501 0.8231	1 0.00031 0.00031 0.0713 0.7897
Sensitivity	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	31.268 < 2e-16 ***	-15.706 4.42e-13 ***	-4.307 0.000312 ***	5.024 5.67e-05 ***	1.196 0.245161	-2.638 0.015372 *
Degrees of freedom Sum of squares Mean square F significance p value		1 2812600001 2812600001 246.6786 4.417e-13 ***	1 211548737 211548737 18.5538 0.0003115 ***	1 287747720 287747720 25.2369 5.669e-05 ***	1 16299819 16299819 1.4296 0.2451615	1 79356916 79356916 6.9600 0.0153721 *
Atorvastatin calcium						
T.plate	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	104.034 < 2e-16 ***	-14.773 < 2e-16 ***	48.259 < 2e-16 ***	3.056 0.00254 **	-9.030 < 2e-16 ***	-2.063 0.04039 *
Degrees of freedom Sum of squares Mean square F significance p value		1 93532936 93532936 521.0503 < 2.2e-16 ***	1 950709285 950709285 5296.1809 < 2.2e-16 ***	1 3955048 3955048 22.0327 4.885e-06 ***	1 33269404 33269404 185.3361 < 2.2e-16 ***	1 1737757 1737757 9.6806 0.002126 **
Retention Time	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	241.76 <2e-16 ***	-149.53 <2e-16 ***	186.62 <2e-16 ***	-28.31 <2e-16 ***	18.86 <2e-16 ***	29.02 <2e-16 ***
Degrees of freedom Sum of squares Mean square F significance p value		1 795.45 795.45 600910.0 < 2.2e-16 ***	1 1216.16 1216.16 918725.1 < 2.2e-16 ***	1 28.48 28.48 21514.1 < 2.2e-16 ***	1 12.34 12.34 9323.0 < 2.2e-16 ***	1 29.42 29.42 22223.8 < 2.2e-16 ***
Tailing Factor	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	30.600 < 2e-16 ***	-1.239 0.217	13.865 < 2e-16 ***	-1.549 0.123	-8.779 5.94e-16 ***	-8.588 2.05e-15 ***
Degrees of freedom Sum of squares Mean square F significance p value		1 0.2069 0.2069 163.48 < 2.2e-16 ***	1 19.4697 19.4697 15387.25 < 2.2e-16 ***	1 0.2191 0.219 173.12 < 2.2e-16 ***	1 7.8648 7.8648 6215.68 < 2.2e-16 ***	1 7.5601 7.5601 5974.91 < 2.2e-16 ***
Resolution	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}

t value p value	29.775 < 2e-16 ***	0.792 0.42953	38.701 < 2e-16 ***	-1.049 0.29551	1.175 0.24146	3.234 0.00142**
Degrees of freedom Sum of squares Mean square F significance p value		1 0.09 0.09 0.2984 0.5854704	1 480.54 480.54 1601.1811 < 2.2e-16 ***	1 0.37 0.37 1.2255 0.2695752	1 0.44 0.44 1.4550 0.2291118	1 3.35 3.35 11.1768 0.0009838 ***
Sensitivity	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	16.223 2.35e-13 ***	-8.028 7.78e-08 ***	-3.018 0.00655 **	2.528 0.01956 *	2.433 0.02398 *	-1.431 0.16702
Degrees of freedom Sum of squares Mean square F significance p value		1 1172506454 1172506454 30320.16 < 2.2e-16 ***	1 165680672 165680672 4284.38 < 2.2e-16 ***	1 116264325 116264325 3006.51 < 2.2e-16 ***	1 107718663 107718663 2785.53 < 2.2e-16 ***	1 37276999 37276999 963.96 < 2.2e-16 ***
Celecoxib						
T.plate	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	222.509 < 2e-16 ***	-21.093 < 2e-16 ***	61.334 < 2e-16 ***	12.738 < 2e-16 ***	-6.807 1.02e-10 ***	-12.758 < 2e-16 ***
Degrees of freedom Sum of squares Mean square F significance p value		1 73957669 73957669 444.928 < 2.2e-16 ***	1 625313952 625313952 3761.875 < 2.2e-16 ***	1 26971296 26971296 162.259 < 2.2e-16 ***	1 7703032 7703032 46.341 1.023e-10 ***	1 27056086 27056086 162.769 < 2.2e-16 ***
Retention Time	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	73.084 < 2e-16 ***	-34.314 < 2e-16 ***	46.416 < 2e-16 ***	2.321 0.0213 *	-0.262 0.7933	2.397 0.0174 *
Degrees of freedom Sum of squares Mean square F significance p value		1 1131.89 1131.89 357942.526 < 2.2e-16 ***	1 2071.11 2071.11 654960.467 < 2.2e-16 ***	1 5.18 5.18 1637.400 < 2.2e-16 ***	1 0.07 0.07 20.921 8.235e-06 ***	1 5.52 5.52 1746.567 < 2.2e-16 ***
Tailing Factor	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	389.916 < 2e-16 ***	1.200 0.2313	-34.722 < 2e-16 ***	-7.323 5.09e-12 ***	3.311 0.0011 **	7.716 4.78e-13 ***
Degrees of freedom Sum of squares Mean square F significance p value		1 0.00050 0.00050 2.7959 0.09602	1 0.42044 0.42044 2339.3195 < 2.2e-16 ***	1 0.01870 0.01870 104.0686 < 2.2e-16 ***	1 0.00382 0.00382 21.2669 6.992e-06 ***	1 0.02076 0.02076 115.5290 < 2.2e-16 ***
Sensitivity	β_0	β_1	β_2	β_{12}	β_{11}	β_{22}
t value p value	2.604 0.0166 *	0.053 0.9580	-0.090 0.9289	0.027 0.9784	0.906 0.3753	-1.393 0.1783
Degrees of freedom Sum of squares Mean square F significance p value		1 6.5368e+07 6.5368e+07 0.0028 0.9580	1 1.8781e+08 1.8781e+08 0.0082 0.9289	1 1.7206e+07 1.7206e+07 0.0007 0.9784	1 1.8872e+10 1.8872e+10 0.8204 0.3753	1 4.4616e+10 4.4616e+10 1.9396 0.1783

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05

Table S3. Determination coefficient (R^2) values for the responses.

R² Value	ATO	CUR	CXB
T.Plate	0.9272	0.8806	0.9561
Retention Time	0.9965	0.9966	0.9409
Resolution	0.9968	-	-

Table S4. Validation of MODR.

Predicted values							
Level	CUR		ATO			CXB	
	Retention time	T. Plates	Retention time	T. Plates	Resolution	Retention time	T. Plates
(-0.2, +0.4)	4.674	7218	5.516	9133	2.246	9.011	12962
(+0.2, +0.8)	4.861	7685	5.862	9497	3.025	9.445	13444
Experimental values (n=3)							
Level	CUR		ATO			CXB	
	Retention time	T. Plates	Retention time	T. Plates	Resolution	Retention time	T. Plates
(-0.2, +0.4)	5.026±0.007	7658±399	5.628±0.004	8779±228	2.561±0.055	8.390±0.008	12708±198
(+0.2, +0.8)	5.082±0.007	8025±439	5.850±0.004	9231±206	3.267±0.037	8.735±0.002	13135±214