

Supplementary Table S1: Regression analysis results for Y₁, Y₂, Y₃ and Y₄ responses

Quadratic model	Adequate precision	R²	Adjusted R²	Predicted R²	SD	% CV	P value
Response Y₁	33.303	0.9661	0.9571	0.9388	2.44	3.14	<0.0001
Response Y₂	66.239	0.9908	0.9884	0.9843	6.54	3.12	<0.0001
Response Y₃	29.866	0.9570	0.9457	0.9226	416.38	5.93	<0.0001
Response Y₄	32.050	0.9669	0.9581	0.9399	1.094E+006	7.42	<0.0001

*R²: coefficient of determination; SD: standard deviation; CV: coefficient of variation.

Supplementary Table S2: Kinetic analysis of MRZ release from different MRZ-NVMs formulations together with MRZ suspension.

Formulation	R2			Mechanism
	Zero	First	Higuchi	
F1	0.8976	0.9688	0.9981	Diffusion
F2	0.8349	0.9261	0.9805	Diffusion
F3	0.849	0.9359	0.9868	Diffusion
F4	0.8359	0.9435	0.9961	Diffusion
F5	0.9173	0.9672	0.9949	Diffusion
F6	0.9166	0.9789	0.9989	Diffusion
F7	0.9179	0.9831	0.9966	Diffusion
F8	0.8385	0.9587	0.9905	Diffusion
F9	0.8724	0.9513	0.9864	Diffusion
F10	0.8424	0.9598	0.9989	Diffusion
F11	0.9112	0.9799	0.9941	Diffusion
F12	0.9246	0.9724	0.9925	Diffusion
F13	0.8627	0.9645	0.9993	Diffusion
F14	0.9308	0.9861	0.9919	Diffusion
F15	0.94	0.9805	0.9958	Diffusion
MRZ susp	0.97014	0.9897	0.9797	First
MRZ-NVM optimum formula	0.91175	0.97613	0.99921	Diffusion
MRZ-free gel	0.97991	0.99389	0.98587	First
MRZ-NVM gel	0.944886	0.988271	0.990142	Diffusion

Supplementary Table S3: The predicted and experimental values of the four responses of the optimum MRZ-NVMs formulation.

Solution	PL90G (%w/v)	Cineole (%v/v)	Ethanol (%v/v)	Y₁ (%)	Y₂ (nm)	Y₃ (%)	Y₄ (µg/cm²)	desirability
Predicted Value	4.81	0.5	5	83.70	221.87	68.79	471.48	0.553
Experimental Value	4.81	0.5	5	81.45 ± 0.53	201.3 ± 4.71	67.29 ± 2.54	468.68 ± 14.31	0.553
Bias%	-	-	-	2.76	10.22	2.24	0.559	-

Each single value represents the average ± (SD) (n=3).

%Bias = (predicted value-Experimental value)/Experimental value