

Supplementary Materials: An Inhalable Theranostic System for Local Tuberculosis Treatment Containing an Isoniazid Loaded Metal Organic Framework Fe-MIL-101-NH₂—From Raw MOF to Drug Delivery System

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Table S1. ANOVA statistics and coefficients for the models obtained by the 2³ factorial design. See section 5.4 and Table 1 for equation terms and factors definitions.

Response		FPF (%)			ED (%)			
Factors	Coefficient Estimate	Mean Square	F Value	p-value	Coefficient Estimate	Mean Square	F Value	p-value
Intercept	0.14	2.034×10^{-3}	129.87	<0.0001	93.62	4.17	16.96	0.0013
A	-2.766E-003	6.121×10^{-5}	3.91	0.0886	0.69	3.80	15.43	0.0044
B	0.024	4.736×10^{-3}	302.45	<0.0001	-	-	-	-
A ²	0.024	1.304×10^{-3}	83.25	<0.0001	-1.44	4.55	18.49	0.0026
Residual	-	1.566×10^{-5}	-	-	-	0.25	-	-
Lack of Fit	-	1.270×10^{-5}	0.55	0.7445	-	0.29	2.41	0.3224
Pure Error	-	2.305×10^{-5}	-	-	-	0.12	-	-
	S.D. *	3.957×10^{-3}	r ² *	0.9824	S.D. *	0.50	r ² *	0.8092
	Mean	0.16	Adj r ² *	0.9748	Mean	92.57	Adj r ² *	0.7615
	C.V. % *	2.46	Pred r ² *	0.9571	C.V. % *	0.54	Pred r ² *	0.6498
	PRESS *	2.663×10^{-4}	Adeq Precision *	22.711	PRESS *	3.61	Adeq Precision *	8.234

* S.D., standard deviation associated with the experimental error; Mean, dependent mean (average of all the values of the response); C.V. %, coefficient of variance of the model; PRESS, Predicted Residual Sum of Squares for the model; r², multiple correlation coefficient; Adj r², r² adjusted for the number of parameters in the model; Pred r², predicted r² is a measure of how the model predicts a response value; Adeq Precision, adequate precision is a measure of the range in predicted response relative to its associated error.



Table S2. 2^3 factorial design for the development of spray-dried INH-MOF loaded MP blend and the respective response parameters (gray rows) and additional data for individual PLGA MPs and LC MPs with different MOF concentrations (white rows). For the preparation a hydrophobic and hydrophilic excipient were used: PLGA and leucin. The blends were obtained changing MOF amount, the PLGA/LC ratio, and blending time. The aerodynamic behavior of the blends was assessed through the TSI test by measuring fine particle fraction (%FPF) and emitted dose (%ED). The content homogeneity of the blends corresponding to each run is also reported. Parameters selected by the model for the final formulation and received responses are shown in the blue row.

Run	Factors				Responses		Content Homogeneity p-value
	A	B		C			
	INH-MOF content [% w/w]	Blending ratio [% w/w]		Blending time [min]	%FPF	%ED	
		PLGA	LC				
1	20	20	80	5	48.06	91.29	0.078
2	20	80	20	5	25.99	90.91	0.840
3	20	20	80	15	46.50	91.90	0.711
4	20	80	20	15	26.86	91.85	0.368
5	40	20	80	5	47.17	93.19	0.103
6	40	80	20	5	28.18	92.00	0.483
7	40	20	80	15	54.78	93.30	0.069
8	40	80	20	15	28.06	92.97	0.380
9	30	50	50	10	52.29	94.01	0.740
10	30	50	50	10	45.75	93.35	0.192
11	30	50	50	10	49.43	93.50	0.128
12	20	100	0	0	11.30	92.53	0.937
13	30	100	0	0	23.20	92.52	0.066
14	40	100	0	0	11.37	96.34	0.361
15	20	0	100	0	53.32	91.99	0.302
16	30	0	100	0	48.77	92.10	0.329
17	40	0	100	0	52.27	92.42	0.157
Final formulation	30	70	70	15	56.65	90.94	0.620

Table S3. Content uniformity data.

Run	Target Content [% <i>w/w</i>]	Actual Content Mean [% <i>w/w</i>]	%RSD (<i>n</i> = 9)	± 10% of Mean
1	20	24.11	3.73	±2.41
2	20	23.41	3.43	±2.34
3	20	25.04	5.93	±2.50
4	20	23.75	3.74	±2.38
5	40	50.77	7.33	±5.08
6	40	49.66	5.32	±4.97
7	40	46.27	2.70	±4.63
8	40	49.99	1.06	±4.99
9	30	27.09	4.63	±2.71
10	30	31.03	4.43	±3.10
11	30	33.55	4.13	±3.35