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Amino-functionalized Zn Metal Organic Frameworks as the Antitumor Drug Curcumin Carriers

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Method

Drug loading

Single factor experiment of IRMOF-1 loaded with curcumin

In this part, the drug loading time single factor test is carried out for the preliminary screening of drug loading time. First, the stirring time of the mixed solution is investigated. 8 mg of curcumin was dissolved in 4 ml of methanol, and then 12 mg of IRMOF-1 was added, and the solution was finally mixed by ultrasound. The mixture was stirred for 3h, 6h, 12h, 24h and 48h respectively. After a certain period of time, the mixture was centrifuged, and the content of curcumin in the supernatant was measured by high performance liquid chromatography. The precipitate was dried under vacuum at 60 °C for 12 hours and then weighed. The drug loading capacity (DLC) was calculated by the following equation.

$$drug\ loading\ capacity = \frac{weight\ of\ drug\ in\ NPs}{weight\ of\ NPs} \times 100\%$$

Then the effect of the weight ratio of IRMOF-1 to curcumin on drug loading was evaluated. Several different weight ratios (3:1, 2:1, 3:2, 1:1, 2:3, 1:2) are selected. After the mixture was stirred for the same time, the drug loading capacity was determined according to the above method.

Orthogonal test of IRMOFs loaded with curcumin

Optimal drug loading conditions are selected through orthogonal test. The drug concentration also has a certain impact on the drug loading capacity. Therefore, the drug loading conditions are optimized based on the three factors of drug loading time, the weight ratio of IRMOFs and curcumin, and the concentration of curcumin. According to the above-mentioned preferred drug loading time and the weight ratio of IRMOFs to curcumin, three levels of orthogonal test were designed. Finally, the drug loading capacity is measured according to the previous steps.

Result

Synthesis and Characterization

Fig. S1 showed the fourier transformed infrared resonance (FT-IR) spectra of two MOFs. The spectra of the two MOFs are generally similar because they have similar structures and groups. Two strong characteristic peaks at 1600-1300 cm-1 proves the existence of -COO bond. The absorption peaks in the fingerprint region (1300 ~ 400cm-1) are in-plane and out-of-plane bending vibrations. They are vibration peaks of the frame structure of IRMOFs. The peak near 523cm-1 is the Zn-O bond absorption peak in the Zn4O tetrahedral metal cluster, which indirectly proves the tetrahedral structure of the crystal. Compared to IRMOF-1, IRMOF-3 introduces amino groups. The characteristic peaks around 3500 cm-1 are caused by primary amine, which proves the presence of amine groups on IRMOF-3.

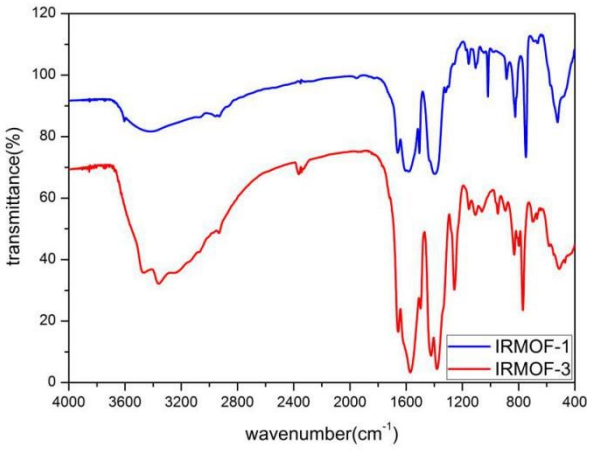

Fig. S1 FTIR spectra of IRMOF-1 and IRMOF-3.

Fig. S2 showed the X-ray diffffraction patterns of IRMOF-1 and IRMOF-3. The three characteristic peaks of IRMOF-1 (2Θ = 9.7°, 13.7°, 15.4°) are in complete agreement with the literature reports. They belong to the (220), (400), (420) crystal planes in the crystal, which further validates the synthesis of IRMOF-1. The two characteristic peaks of IRMOF-3 (2Θ = 6.8°, 9.6°) are in good agreement with those reported in the literature. It is further verified that the synthesized crystal is IRMOF-3 with good crystallinity.

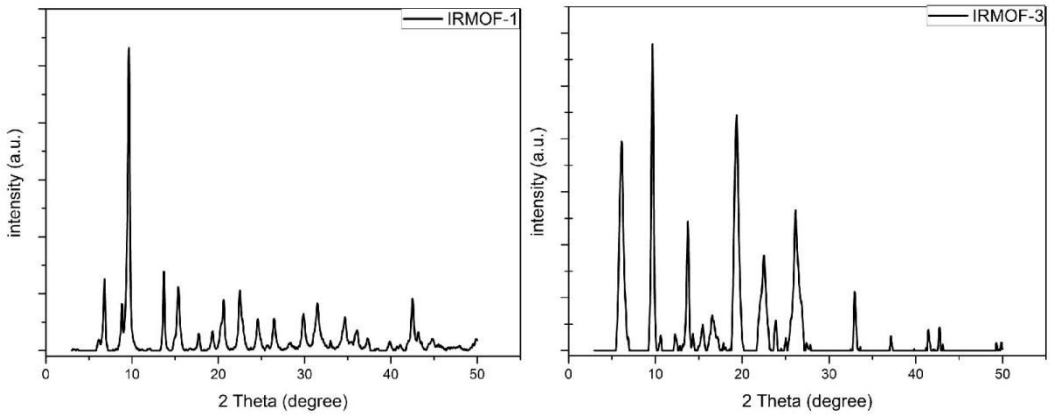

Fig. S2 X-ray diffffraction patterns of IRMOF-1 and IRMOF-3.

Drug loading

Single factor experiment of IRMOF-1 loaded with curcumin

The effect of drug loading time on drug loading capacity is shown in Fig. S3. With the extension of the drug loading time, the drug loading capacity gradually increases. However, when the drug loading time exceeds 24 hours, the increase in drug loading capacity is not significant, and it is speculated that the drug adsorption has reached dynamic equilibrium. Therefore, we choose 6h, 12h, and 24h as the three levels of drug loading time in the orthogonal test.

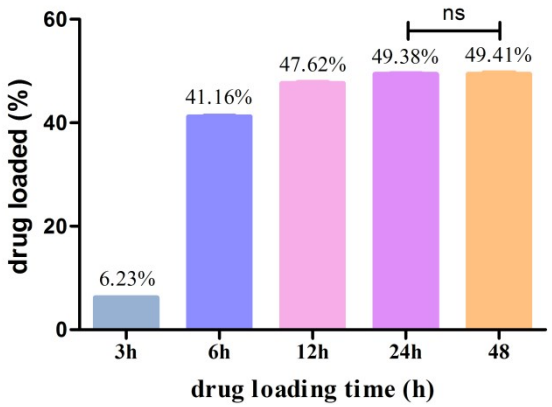

Fig. S3 drug loading capacity for different drug loading time

The ratio of IRMOF-1 to curcumin has a significant effect on the drug loading, and as the ratio of curcumin increases, the drug loading capacity gradually increases. When the ratio of curcumin increased to 3/5, the drug loading capacity no longer increased. Therefore, we choose the three ratios of 3:2, 1:1,2:3 (the ratio of IRMOF-1 to curcumin) as the three levels in the orthogonal experiment. The effect of the ratio of IRMOF-1 to curcumin on drug loading capacity is shown in Fig. S4.

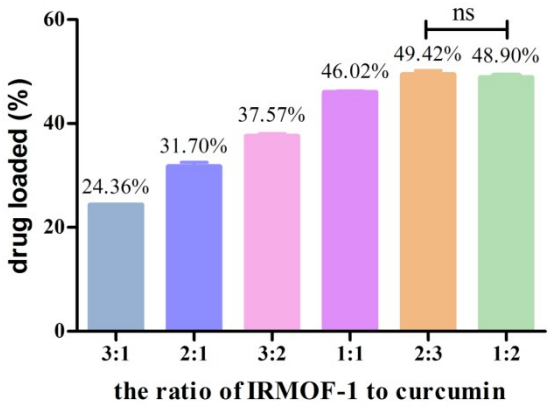

Fig. S4 drug loading capacity for different ratio of IRMOF-1 to curcumin

Orthogonal test of IRMOFs loaded with curcumin

Due to the low solubility of curcumin, there are fewer levels of factors to choose from, so single factor investigation of curcumin concentration is not carried out. In theory, the greater the concentration of the drug, the higher the drug loading. Therefore, we choose the three highest possible concentrations as the three levels of the drug concentration factors in the orthogonal test. According to the above single factor experiment results, the orthogonal experiment was designed, and the factor level table is shown in Table S1. For IRMOF-1, the orthogonal result table is shown in Table S2, and the analysis of variance is shown in Table S3. For IRMOF-3, the orthogonal result table is shown in Table S4, and the analysis of variance is shown in Table S5.

Table S1. table of the factor level

	factor		
	A	B	C
level	Drug loading time (h)	the weight ratio of IRMOFs and curcumin	Cur concentration (mg/ml)
1	6	3:2	1
2	12	1:1	2
3	24	2:3	3

Table S2. the orthogonal result for IRMOF-1

Serial number	A	B	C	DLC/%
1	2	1	3	17.482
2	2	3	2	19.876
3	1	3	3	20.659
4	3	3	1	17.743
5	1	1	1	15.646
6	2	2	1	16.101
7	3	1	2	38.196
8	3	2	3	47.628
9	1	2	2	16.242
K1	17.516	23.775	16.497	
K2	17.820	26.657	24.771	
K3	34.522	19.426	28.590	
R	17.006	7.231	12.093	

Table S3. the analysis of variance (IRMOF-1)

Source of Variance	Sum of squared deviations	Degree of freedom	variance	F value	P
A	568.298	2	284.149	3.152	0.241
B	79.506	2	39.753	0.441	0.694
C	229.290	2	114.645	1.272	0.440
error	180.299	2	90.149		

Table S4. the orthogonal result for IRMOF-3

Serial number	A	B	C	DLC/%
1	2	1	3	47.58
2	2	3	2	48.14
3	1	3	3	44.20
4	3	3	1	49.40
5	1	1	1	9.37
6	2	2	1	43.98
7	3	1	2	48.14
8	3	2	3	52.26
9	1	2	2	23.21
K1	25.593	35.030	34.250	
K2	46.560	39.817	39.830	
K3	49.933	47.247	48.013	
R	24.340	12.217	13.763	

Table S5. the analysis of variance (IRMOF-3)

Source of Variance	Sum of squared deviations	Degree of freedom	variance	F value	P
A	1043.651	2	521.825	8.748	0.103
B	227.364	2	113.682	1.906	0.344
C	287.533	2	143.766	2.410	0.293
error	119.295	3	59.648		

P value less than 0.05 is significant difference, less than 0.01 is extremely significant. For IRMOF-1, taking the drug loading as the indicator, the results of the variance analysis showed that A (drug loading time),

B (weight ratio), and C (Cur concentration) had no significant effects, and the influence of each factor on the experimental results was A>C>B. According to the intuitive analysis of the orthogonal table, the optimal drug loading conditions are: $A_3B_2C_3$, that is, drug loading for 24 hours, the weight ratio of IRMOF-1 to Curcumin is 1:1, and Cur concentration is 3mg/ml. And for IRMOF-3, the optimal drug loading conditions are: $A_3B_3C_3$, that is, 12 hours of drug loading, the weight ratio of IRMOF-3 to Cur is 2:3, and the concentration of Cur is 3mg/ml.

Then the optimal drug loading conditions were selected for the curcumin loading to verify the results of the orthogonal test. For IRMOF-1, the curcumin loading capacity is 49.30%. And for IRMOF-3, the curcumin loading capacity is 55.36%.