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Original Research Article

Application of Taguchi orthogonal array in optimization of the synthesis and crystallinity of metal-organic framework-5 (MOF-5)

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Abstract

Purpose: *To use the L25 Taguchi orthogonal array for optimizing the three main solvothermal parameters that affect the synthesis of metal-organic frameworks-5 (MOF-5).*
Methods: *The L25 Taguchi methodology was used to study various parameters that affect the degree of crystallinity (DOC) of MOF-5. The parameters comprised temperature of synthesis, duration of synthesis, and ratio of the solvent, N,N-dimethyl formamide (DMF) to reactants. For each parameter, the volume of DMF was varied while keeping the weight of reactants constant. The weights of 1,4-benzodicarboxylate (BDC) and $Zn(NO_3)2.6H_2O$ used were 0.390 g and 2.166 g, respectively. For each parameter investigated, five different levels were used. The MOF-5 samples were synthesized using the solvothermal reaction method, and successful synthesis was confirmed with x-ray diffraction (XRD), microscopy, Fourier transform infrared spectroscopy (FTIR) and energy-dispersive x-ray spectroscopy (EDS). The DOC obtained via XRD served as a parameter of objective quality.*
Results: *The optimum conditions that gave the highest DOC were synthesis temperature of 130 °C, duration of 60 h, and a vehicle volume of 50 mL, with optimum Brunauer-Emmett-Teller surface area (BET -SA) of 800 m^2/g. All the three synthesis parameters significantly influenced the DOC of the synthesized MOF-5 ($p < 0.05$). Sub-optimal conditions resulted in distorted MOFs, products that deviated from MOF-5 specifications, or MOF-5 with low DOC.*
Conclusion: *Based on DOC and BET-SA, the best conditions for synthesis of MOF-5 when using Taguchi OA, were temperature of 130 °C, duration of 60 h, and a DMF volume of 50 mL.*

Keywords: *MOF-5, Taguchi orthogonal array, XRD, Crystallinity*

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INTRODUCTION

Metal-organic frameworks (MOFs) are a novel class of materials in which the metal ion serves as a coordinating core and is coupled to many polyatomic organic molecules to create structures with three-dimensional properties [1]. In the last three decades, MOFs have become increasingly popular as research materials in the disciplines of chemistry, pharmaceutics, physics, materials science, and engineering. They have been utilized in gas separation and storage, sensing, catalysis, analytical chemistry, and drug delivery. By selecting metal cores and linkers, it

is possible to adjust the physicochemical characteristics of the produced MOFs, such as degree of crystallinity (DOC), surface area, pore size, and diameter, according to the desired application [2].

Drug targeting, control of drug release, and enhancement of drug stability are the most common applications of MOFs in drug delivery. In such applications, the drugs are usually stabilized within the porous structure of MOFs, and the release is triggered by various stimuli such as the nature and pH of the media, temperature, pressure, or even magnetic stimulation [3].

The main factors to be considered when selecting MOFs for drug delivery are the capacity to decompose and release the drug in the desired profile in appropriate medium, an acceptable toxicity profile, and an appropriate match between the pore size of the MOF and the resident drug [3].

Figure 1 shows the chemical formula of one water-soluble MOF which is MOF-5 ($Zn_4O(BDC)_3$ (BDC = 1,4-benzodicarboxylate). The cubic, porous framework is built from $(Zn4O)^{+6}$ clusters and linked through BDC^{-2} ligands [4]. Zinc is a relatively safe metal (lethal dose (LD_{50}) ≈ 3 g/kg) that is widely used in nutritional supplements [5]. 1,4-Benzodicarboxylate (BDC, also known as terephthalic acid) is an organic linker with low oral toxicity and a high safety profile (LD_{50} in mouse > 1 g/kg) [6]. The MOF-5 structure shows a relatively large pore size of approximately 12.5 Å in diameter, which makes it suitable for binding small-molecule drugs [3].

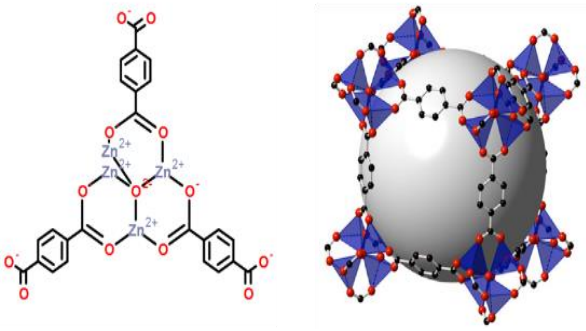

Figure 1: Structure of MOF-5 [4]

Different solvothermal, microwave, and sono-chemical procedures have been used for the preparation of MOF-5. Most frequently, MOF-5 is prepared using the solvothermal method. This approach utilizes a temperature higher than the boiling point of the reaction vehicle used, and it is usually performed inside sealed reactors to allow for pressure build-up [7,8]. The solvothermal method usually has a higher yield and crystallinity than the other methods [2]. The starting materials for MOF-5 synthesis are zinc nitrate hexahydrate ($Zn(NO_3)_2.6H_2O$) or zinc acetate dihydrate as metal source, and BDC as the organic connector. The vehicle is usually N,N-dimethylformamide (DMF). The main factors that affect the properties of synthesized MOF-5 are reaction duration, reaction temperature, and metal/ligand ratio [9]. The reported conditions for synthesis of MOF-5 vary from 80 to 140 °C, with durations of 12 to 72 h. The produced MOF-5 are ideally cuboid in shape, with surface areas ranging between 260 and 4400 m^2/g [10,11].

One important property of MOFs is crystallinity. Crystalline MOFs have well-defined pore sizes and shapes which are tailored for specific applications, unlike amorphous MOFs which are less useful. Moreover, crystalline MOFs are more stable than amorphous MOFs and are less likely to break down or lose their structures over time [12]. In this study, the synthesis parameters of MOF-5 were systematically investigated and optimized to obtain MOFs with the highest DOC.

EXPERIMENTAL

Materials

Zinc nitrate hexahydrate ($Zn(NO_3)_2.6H_2O$) was purchased from Central Drug House, India. 1,4-Benzene dicarboxylic acid (BDC) was obtained from Reagent World, USA. Both DMF and chloroform were purchased from Alpha Chemika, India. Solvothermal synthesis autoclave reactors lined with polytetrafluoroethylene were products of Xiamen Ollital Technology Co. Ltd., China.

Methods

Design

The Taguchi experimental methodology was used to study various experimental parameters affecting the DOC of MOF-5. In the literature, the two main synthesis parameters that affect the DOC of MOFs have been identified as solvothermal temperature and duration of synthesis [11]. One unique parameter investigated in this study is the ratio of solvent (DMF) to starting materials. For this specific parameter, the volume of DMF was varied while keeping the weights of reactants constant. The weights used for each formula were 2.166 g for $Zn(NO_3)_2.6H_2O$, and 0.390 g for BDC. For each of the three parameters investigated, five different levels were used. The range of levels was defined based on a literature review and

preliminary experiments. Table 1 shows the parameters and the various levels used.

Table 1: The three parameters investigated in the synthesis of MOF-5

Parameter	Level				
	1	2	3	4	5
Temperature (°C)	90	100	110	120	130
Duration (h)	12	24	36	48	60
Volume of DMF (mL)	20	30	40	50	60

The L25 orthogonal array (OA) of Taguchi was constructed for various parameters and their levels, as shown in Table 2.

Table 2: Synthesis parameters for the L25 experimental work plan

Formula	Temperature (°C)	Duration (h)	Volume of DMF (mL)
T1	90	12	20
T2	90	24	30
T3	90	36	40
T4	90	48	50
T5	90	60	60
T6	100	12	30
T7	100	24	40
T8	100	36	50
T9	100	48	60
T10	100	60	20
T11	110	12	40
T12	110	24	50
T13	110	36	60
T14	110	48	20
T15	110	60	30
T16	120	12	50
T17	120	24	60
T18	120	36	20
T19	120	48	30
T20	120	60	40
T21	130	12	60
T22	130	24	20
T23	130	36	30
T24	130	48	40
T25	130	60	50

Following analysis of the Taguchi method (as indicated in Results section), additional 12 formulas were synthesized using all possible combinations of the optimum two levels of temperature, three levels of duration, and two levels of volume. These additional formulas were designated OP1 - OP12 (Table 3).

Synthesis of MOF-5

The MOF-5 samples were synthesized using the solvothermal reaction method described in the literature [9,11].

Table 3: Synthesis parameters for optimization of formulas

Formula	Temperature (°C)	Duration (h)	Volume of DMF (mL)
OP1	120	36	50
OP2	120	48	50
OP3	120	60	50
OP4	120	36	60
OP5	120	60	60
OP6	130	36	50
OP7	130	48	50
OP8	130	60	50
OP9	130	36	60
OP10	130	60	60
OP11	120	48	60
OP12	130	48	60

Note: Orthogonal array (OA) of Taguchi, analysis of variance (ANOVA), and regression analysis were performed using Minitab® statistical software version 21.2 (2022)

Briefly, 2.16 g of $Zn(NO_3)_2.6H_2O$ and 0.39 g of BDC were dissolved separately in the specified volumes of DMF, as shown in Table 2 and Table 3. Then, the mixtures were stirred to dissolution (within an average of 30 min). Then, each solution was placed in a 100-mL solvothermal reactor lined with polytetrafluoroethylene and put in an oven for the corresponding duration specified. Thereafter, the reactors were allowed to cool to room temperature. Each mixture was centrifuged at 4000 rpm, and the solid was extracted through decantation and washed twice with DMF. The powder was then soaked in chloroform for 3 days, and the chloroform was refreshed every day. The resultant powder was dried under vacuum at 80 °C and preserved in a vacuum de-gassing chamber.

Characterization of MOF-5

X-ray diffraction (XRD)

The XRD diffractograms of MOF-5 samples were obtained using a DX-2700BH diffractometer (Dandong Haoyuan Instrument, China) with a copper Kα radiation source (30 kV and 20 mA) at a wavelength (λ) of 1.54056 Å, and at 2-theta (2θ) scanning range of 5 – 50 degrees. The DOC was calculated as the ratio of the area under the characteristic peak to the total area under the XRD curve, using OriginPro software, version 9.8.5.204 (2021).

Microscopy

Optical microscopy was done using an Olympus CX21 optical microscope, Japan. Field emission scanning electron microscopy (FE-SEM) was performed using the Inspect F50 microscope

(FEI, USA) under pressure of 1.25 x 10^{-2} Pa at 30 kV.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum was obtained at room temperature between 400 – 4000 cm^{-1} via KBr disc methodology using the Lambda 7600 FTIR spectrometer (USA).

Brunauer-Emmett-Teller surface area (BET-SA) analysis

The pore volumes and surface areas were obtained *via* nitrogen adsorption/desorption at 77 K using the ASAP 2020 surface area analyzer (Micromeritics Instrument Corporation, USA). A vacuum drying oven (Model DZ-1BC, Faithful Instruments, China) was used in the activation of MOFs to remove moisture and certain atmospheric gases that create hindrance and reduce surface area [13]. The activation was done at 70 °C for 12 h, followed by activation at 120 °C for 2 h under dynamic vacuum.

Energy-dispersive X-ray spectroscopy (EDS)

The chemical composition of MOF-5 was determined with EDS using Axia ChemiSEM (Thermo Fisher Scientific, Netherlands) at an acceleration voltage of 30 kV.

RESULTS

X-ray diffraction pattern

The objective quality parameter used in this study was the percentage of DOC obtained with XRD. A total of 25 diffractograms were initially obtained for the L25 OA of Taguchi (Figure 2). This was followed by 12 diffractograms for the optimization process (Figure 3). It was noticed that by varying synthesis parameters, shifting of peaks to a different 2θ position occurred. In addition, the disappearance of characteristic peaks and/or the appearance of new unknown peaks also took place in some formulas. These events affected the DOC of the formulas, as the calculations included characteristic (fingerprint) peaks of MOF-5.

The characteristic peaks of MOF-5 were at 2θ values of 6.9, 8.8, 9.76, 13.8, 15.5, 17.8, 19.4, 20.6, 22.6, 24.6, 26.5, 29.9, 31.6, 34.62, 36.1, 42.7, 44.8, and 47.5 [11,12]. These peaks were used to calculate the DOC using Eq 1 [7]. Table 4 shows the DOC of the initial formulas (L25 OA of Taguchi) and optimized formulas.

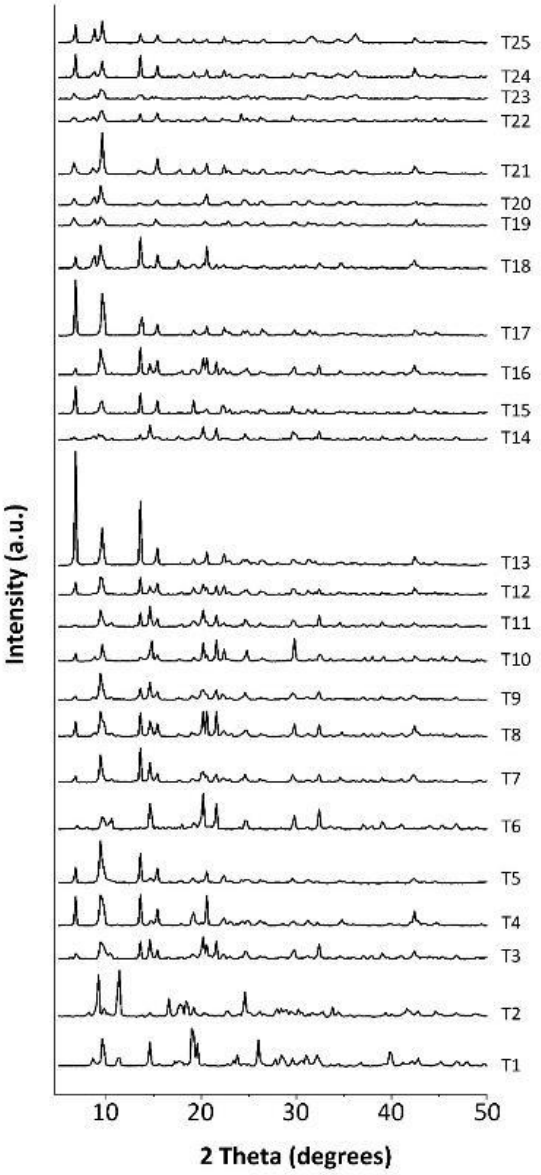

Figure 2: XRD of L25 OA of Taguchi formula

DOC = $(\sum A/A_o)100$ ..... (1)

Where $\sum A$ = sum of areas under characteristic peaks and A_o = total area under the curve.

Effect of synthesis parameters on DOC

In the present study, the values of DOC were analyzed as the higher-the-better for enhancing the stability and uptake of MOF-5, using Minitab® statistical software. The signal-to-noise (S/N) ratio was calculated using Eq 2 [14].

S/N for the higher the better = $-10\left(\mathrm{Log}\frac{1}{n}\sum_{i=1}^{n}\frac{1}{Y_i^2}\right)$ ..... (2)

where Y is the observed data for each response, n is the number of observed data, and Y_i is the i^{th}

observed data. Table 5 shows the S/N ratio response Table for the DOC, while Figure 4 shows the effect of synthesis parameters on DOC.

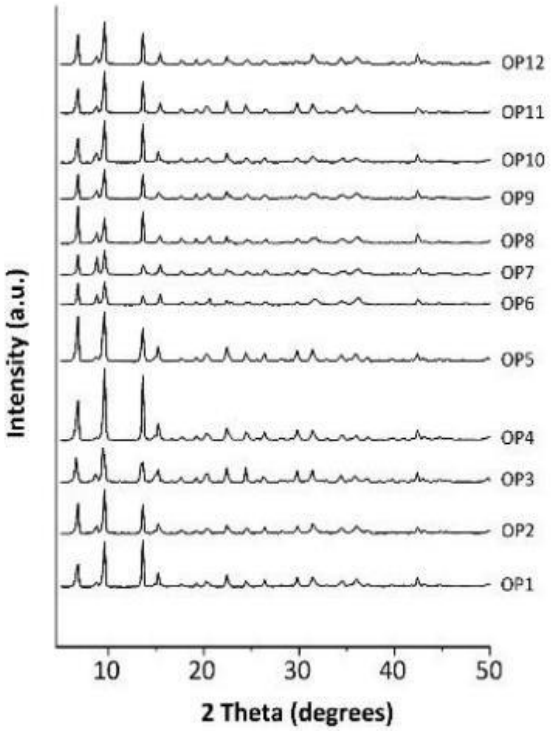

Figure 3: XRD of optimized formula showing characteristic peaks of MOF-5

Temperature had the greatest impact on DOC, according to rank in Table 5, followed by duration, while the amount of DMF in a sample had the least impact on DOC. These effects were confirmed using ANOVA.

Temperature

It was observed that DOC increased with increasing temperature, especially between 100 and 120 °C. Figure 4 also shows that increasing the temperature above 120 °C did not markedly improve the DOC. However, 130 °C was included in the optimization.

Duration of synthesis

The duration of synthesis was shown to have a linear relationship with DOC. Results showed that the highest DOC was achieved when the synthesis duration was 60 h (Figure 4). Figure 5 shows optical microscopic images of T25 (the formula with the highest DOC), T10, and other preliminary formulas prepared at a duration of 72 h.

Table 4: DOC of all synthesized formula

Formula	Crystallinity (%)
T1	29.3
T2	27.9
T3	48.8
T4	69.0
T5	65.7
T6	37.9
T7	50.2
T8	51.1
T9	58.2
T10	43.8
T11	50.1
T12	57.7
T13	56.0
T14	46.6
T15	65.2
T16	56.1
T17	61.8
T18	67.1
T19	70.3
T20	73.3
T21	69.1
T22	58.8
T23	62.8
T24	64.2
T25	74.4
OP1	66.9
OP2	69.8
OP3	71.1
OP4	66.2
OP5	73.0
OP6	72.7
OP7	71.5
OP8	67.5
OP9	72.2
OP10	68.2
OP11	71.3
OP12	70.2

Table 5: Response table for signal-to-noise ratios (DOC the-higher-the-better)

Level	Temperature (°C)	Duration (h)	Volume of DMF (mL)
1	33.02	33.33	33.49
2	33.58	33.87	33.93
3	34.77	35.08	35.05
4	36.32	35.71	35.72
5	36.34	36.04	35.84
Delta	3.32	2.71	2.35
Rank	1	2	3

Ratio of synthesis vehicle to reactants

The volume of DMF varied from 20 to 60 mL per formula. Figure 4 shows that there was a linear relationship between the DOC and the volume up to 50 ml. In addition, the use of 60 mL increased DOC, but to a lesser extent than previous increments. The two volumes (50 and 60 mL) were used in the optimization process.

Table 6: ANOVA for degree of crystallinity (DOC)

Source	Sum of squares	Mean squares	*F*-value	*P*-value	Contribution (%)
Temperature (°C)	1401.8	1401.77	31.19	0.000015	38
Duration (h)	897.6	897.59	19.97	0.000212	22
DMF Volume (mL)	610.0	610.04	13.57	0.001379	18

Regression analysis and ANOVA

Regression analysis was used to arrive at a regression equation for DOC with respect to the three parameters investigated. The DOC was computed using Eq 3.

DOC (%) = -28.3 + (0.5295 x temp. (°C) + (0.3531 x duration (h)) + (0.3493 x DMF volume (mL) …… (3)

The R^2 value for the regression equation was 75.51 %. The ANOVA for DOC is shown in Table 6. It was found that DOC was most affected by synthesis temperature, followed by the duration of synthesis. The least factor that affected DOC was the volume of DMF. The percentage contributions of synthesis temperature, duration of synthesis, and volume of DMF were 38, 22, and 18, respectively, as shown in Table 6. Each of the three parameters significantly influenced DOC ($p < 0.05$).

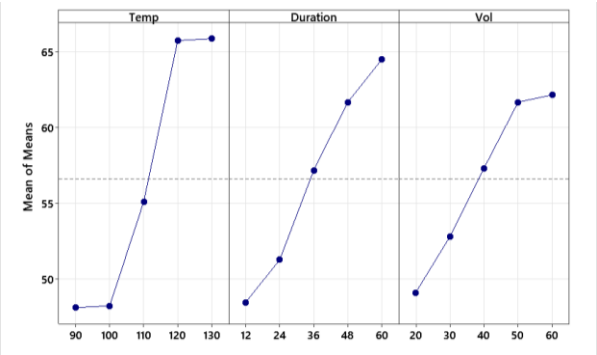

Figure 4: Effect of synthesis parameters on DOC

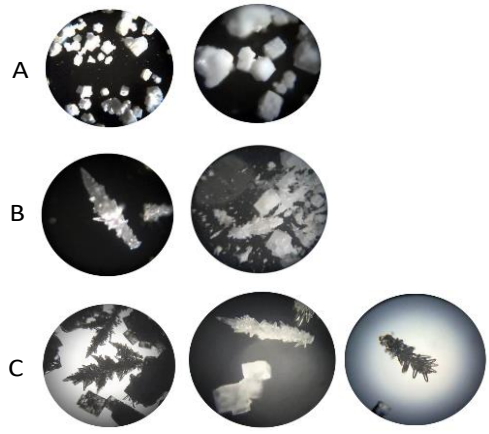

Figure 5: Optical microscopic images of T25 (A), T10 (B), and a preliminary formula synthesized for 72 h (C)

Table 7: The top 5 formula with respect to their DOC

Formula	Temp (°C)	Duration (h)	Volume of DMF (mL)	DOC (%)
T25	130	60	50	74.4
T20	120	60	40	73.3
OP5	120	60	60	73.0
OP6	130	36	50	72.7
OP9	130	36	60	72.2

Temp = Temperature

OPTIMIZATION

Table 3 shows the synthesis parameters corresponding to the optimized formulas. Three levels were taken for duration rather than two because, at 60 h, some formulas had deformed MOF morphology (Figure 5). The XRD was carried out on these 12 optimized formulas, and their DOC values were calculated. The DOC results are shown in Table 4. After arranging all Taguchi 25 formulas and the 12 optimization formulas with respect to DOC values, it was found that the highest DOCs were in T25, T20, OP5, OP6, and OP9. Their synthesis conditions are indicated in Table 7.

BET-SA

Six formulas were tested for BET-SA based on coverage of the various DOCs. The surface areas and pore volumes are shown in Table 8, along with the corresponding DOCs. It was observed that the surface area and pore volume increased with increase in DOC.

Table 8: Surface areas and pore volumes of selected MOF-5 formulas

Formula	DOC (%)	BET-SA (m^2/g)	Pore volume (cm^3/g)
T2	27.9	75.4	0.066
T1	29.3	107.8	0.075
T7	50.2	116.5	0.086
T17	61.8	134.5	0.106
T18	67.1	285.1	0.234
T25	74.4	800.0	0.369

EDS

The chemical composition of the optimum formula (T25) was evaluated using EDS. This examination clearly demonstrated the identification of prominent peaks of the elements

carbon (C), oxygen (O), and zinc (Zn) (Figure 6). The EDS examination showed absorption bands with peaks at 1.0, 8.6, and 9.6 keV.

FTIR

Figure 7 shows the comparison between the reported spectrum and the synthesized T25 formula. A tetrahedral node of Zn_4O was found at ≈522 cm^{-1} representing Zn – O vibration. The BDC linker had vibrational modes due to the carboxylic groups (-COOH) linked to Zn and the benzene (C_6H_6) ring. The out-of-plane bending (819, 749, and 668 cm^{-1}) and in-plane bending (1152, 1105, and 1016 cm^{-1}) vibration modes of the C-- H bond imply the existence of C_6H_6. Bands at 1580 and 1380 cm^{-1} were due to C--O asymmetric and symmetric vibrations of –COOH groups, respectively. The hydrolysis of zinc nitrate produced $Zn(OH)_2$. This had, in addition to H_2O, an O – H broad band vibration at ≈3340 cm^{-1}.

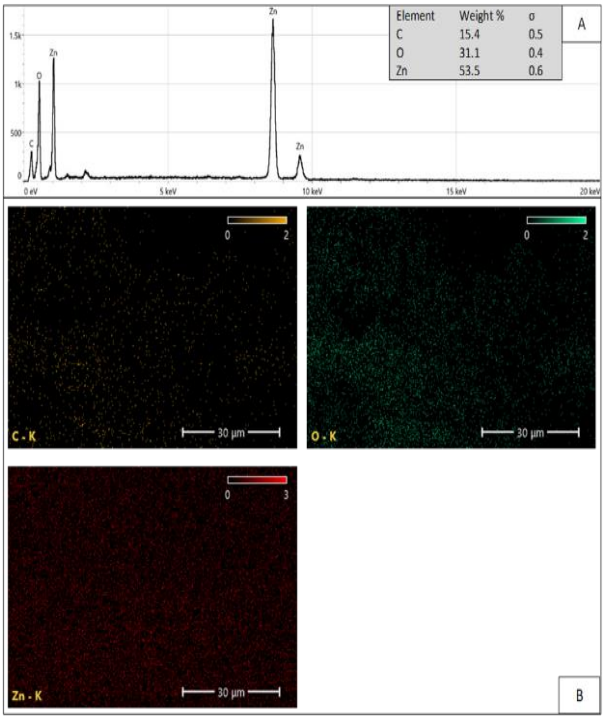

Figure 6: EDS (A) and elemental mapping (B) of the optimum formula (T25)

Microscopy

Optical microscopy was performed for each synthesized formula in order to continuously evaluate the formation of typical MOF-5 cubes or structural deformities. It was noticed that formulas with low DOC were usually malformed, resulting in different morphologies. Some of the optical microscopic images along with the FE-SEM of T25 are shown in Figure 8 and Figure 9.

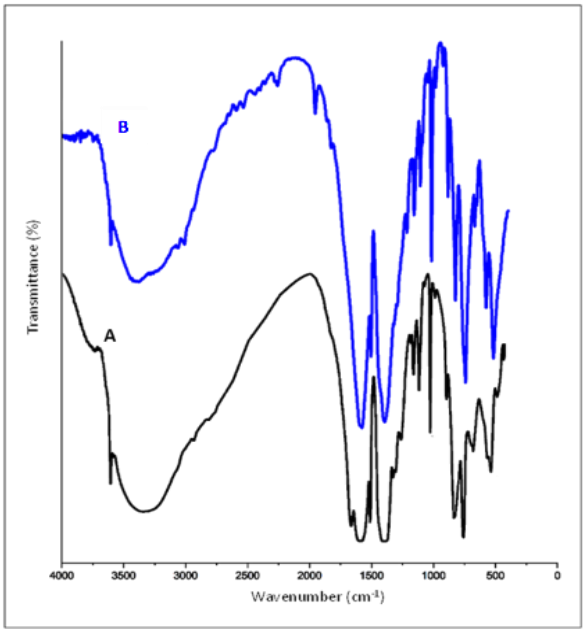

Figure 7: FTIR diagrams of MOF-5 (A) and T25 (B)

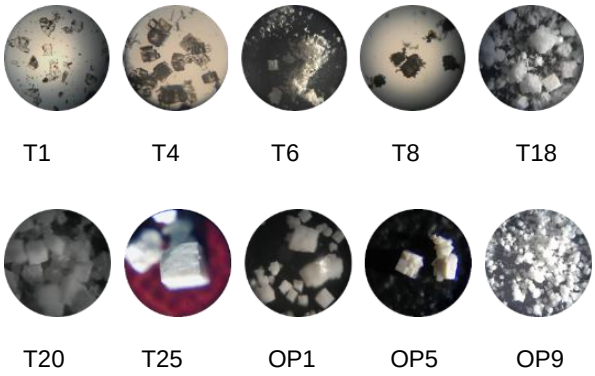

Figure 8: Optical microscopic images of some formula (see also Figure 5)

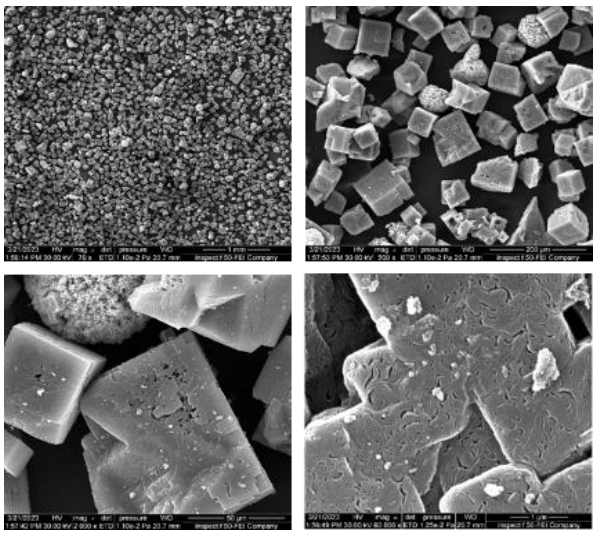

Figure 9: FE-SEM images of the prepared T25 formula

DISCUSSION

This study is the first investigation on the effect of key parameters on synthesis of MOFs using Taguchi OA. The objective parameter for quality was the DOC obtained using XRD. With respect to S/N ratio, the optimized parameters that gave rise to the highest DOC of 74.4 % were synthesis temperature of 130 °C, duration of 60 h, and a vehicle volume of 50 mL, with optimum Brunauer-Emmett-Teller surface area (BET-SA) of 800 m^2/g. Temperature had the most significant effect. The difference between the target signal (wanted value mean) and experimental background noise (unwanted value standard deviation) is referred to as the signal-to-noise (S/N) ratio [15]. Taguchi [15,16] has classified the S/N ratio into three categories: the lower-the-better, the medium-the-better, and the higher-the-better. In the present study, the values of DOC were analyzed as the higher-the-better.

Relatively little is known about the specific phases of crystallization of MOFs, although their significance is recognized in several applications. However, the most common explanations are two of the contrasting views that have been put forth to account for their nucleation and development. The first one takes the conventional route by which MOF crystals develop via the attachment of monomers to naturally-occurring stable crystalline nuclei. The second pathway suggests that MOFs form through a multistep, non-classical process in which monomers in solution first organize into small clusters comprising metal ions and linkers. Subsequently, these clusters combine into amorphous nanoparticles from which crystallization emerges. The absence of appropriate experimental methods that directly trace the growth of individual crystals is a challenge to the determination of the various stages of MOF nucleation, which is crucial for settling the debate around the various nucleation processes [17].

Wang *et al* [18] reported the influence of increasing temperature on the morphology and thermal stability of MOF-5. They concluded that increasing the solvothermal synthesis temperature increased thermal stability and changed the shape of MOFs from sheet-like to cuboid. When the synthesis is performed in a closed system at a high temperature, pressure will build up, and both factors will enhance the possibility of crystallization. This is so because the solubility would increase, reaching a supersaturation status, and the molecules of reactants would interact more closely with each other [19]. Cheetham *et al* [20] suggested that an increase in temperature increases the product density, dimensionality, and number of linked metallic ions per ligand, while the degree of hydration is decreased. The release of water molecules entrapped within the solid-state leads to entropic gain which is thought to be the main driving force for such behavior. As a result, ligands bind to the vacant coordination sites on the metal, thereby increasing the connection between metal centers, and densifying the framework at the same time.

The second most important factor for optimized synthesis of MOF-5 was duration of synthesis. Increasing the duration of MOF-5 synthesis increased the DOC by allowing more time for the molecules to interact and form stronger bonds. This led to more ordered and crystalline structures and, therefore, a higher DOC. However, it has been reported that prolongation of the synthesis process of MOFs may lead to deformation of their crystal morphology. This may be attributed to the re-dissolution of the MOFs [21]. In the case of MOF-5, increasing duration beyond 60 h was shown to distort the shape of crystals from cuboid to arrowhead with irregular spikes, especially when using small volumes of DMF.

The effect of solvent on MOF-5 synthesis was also significant, although its impact was the least. Solvents influence the formation and DOC of MOFs by affecting the solvation and regulation of the self-assembly environment. As the volume of reaction medium increases, the solubility of reactants increases, thereby allowing more molecules to interact, resulting in a higher DOC [19].

With respect to optimization, the Taguchi method has a limitation in that the results obtained may be relative and may not exactly reflect the parameter with the highest degree of influence on the outcome [22]. Accordingly, determination of the optimum synthesis conditions was carried out with additional 12 formulas for all possible combinations of the best temperatures (120 and 130 °C), DMF volumes (50 and 60 mL), and durations (36, 48, and 60 h).

It was observed that the surface area and pore volume increased with increases in DOC. This was so because as the MOFs become more crystalline, their pores become more uniform, regular, and interconnected, enabling gas molecules to pass through the MOF more easily and to get adsorbed onto more sites. In addition, increased order at higher DOC reduces surface defects which may block internal surface access.

With fewer defects and a more ideal structure, more MOF surface becomes available, thereby increasing BET surface area. Moreover, it has been demonstrated that increasing the DOC of MOFs reduces the pore sizes, thereby increasing the BET-SA and pore volume [23].

In this study, the absorption band peaks at 1.0, 8.6, and 9.6 keV were indicative of typical zinc metallic absorption. It also showed typical peaks of O and C at 0.5 and 0.26 keV, respectively. The results of composition analysis of T25 were consistent with those reported previously for MOF-5 [11]. In addition, the spectrum of different formulas obtained matched the previously reported spectra. The band seen at ≈3605 cm^{-1} was most likely due to the existence of DMF [24].

CONCLUSION

This is the first study on the influence of synthesis parameters on MOFs utilizing Taguchi OA. Based on DOC and BET-SA, the best conditions for synthesis of MOF-5 were temperature of 130 °C, a duration of 60 h, and DMF volume of 50 mL. Sub-optimal conditions result in distorted MOFs, products that deviate from MOF-5 specifications, or MOF-5 with low DOC. The three factors significantly affecting the DOC were in the order: temperature > duration > ratio of synthesis vehicle to reactants.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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