# OPTIMIZATION OF SYNTHESIS PARAMETERS AND CHARACTERIZATION OF 4,6-DIHYDROXY-2-METHYL PYRIMIDINE

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## Abstract

4,6-dihydroxy-2-methylpyrimidine (MPD) serves as a crucial precursor in the pharmaceutical industry and the synthesis of organic compounds and has recently gained attention as a key intermediate in the production of the energetic material FOX-7. A modern synthetic approach involves the condensation of acetamidine hydrochloride ($C_2H_6N_2$·HCl) and diethyl malonate ($C_7H_{12}O_4$) in an organic alkaline medium; however, limited data are available regarding the technological parameters that govern this process. In this study, the Taguchi experimental design method was employed to determine the optimal conditions for maximizing MPD yield. Validation experiments confirmed that the optimal parameters included a sodium methoxide concentration of 18%, a reaction time of 180 minutes, and a DEM/Ace·HCl molar ratio of 1.4. Under these conditions, a maximum MPD yield of 88.5% was achieved. The synthesized MPD was subsequently identified and characterized through nuclear magnetic resonance (NMR) spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, and melting point determination. Additionally, powder X-ray diffraction (PXRD) analysis was conducted, with the PXRD pattern of MPD being reported for the first time, providing valuable structural insights into the synthesized compound.

***Keywords:*** *4,6-dihydroxy-2-methylpyrimidine; MPD; Taguchi method; FOX-7.*

## 1. Introduction

In recent years, the development and utilization of safer explosives have been of growing interest to many advanced nations [1]. 1,1-diamino-2,2-dinitroethylene (FOX-7), a low-sensitivity explosive compound, was first synthesized in 1998 by the Swedish Defence Research Agency (FOI) [2]-[4]. Since its discovery, significant attention has been directed toward this compound by researchers [5]-[7]. Among the various synthetic approaches investigated for FOX-7 production, the direct nitration of 4,6-dihydroxy-2-methylpyrimidine (MPD) has been recognized as a highly efficient and safe method [8].

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The first synthesis of MPD was reported in 1940 by L. P. Ferris and A. R. Ronzio [9] through the condensation of acetamidinium chloride ($C_2H_6ClNO$) and diethyl malonate in a sodium methoxide ($CH_3ONa$) solution. However, several limitations were associated with this method, including a low yield (43%), the use of $C_2H_6ClNO$, which is difficult to obtain, highly toxic, and unstable, and a prolonged reaction time of three days.

To improve synthetic efficiency and reduce production costs, a more favorable approach has been developed using acetamidine hydrochloride (Ace·HCl) and diethyl malonate (DEM), as outlined in the following reaction [10] (Fig. 1):

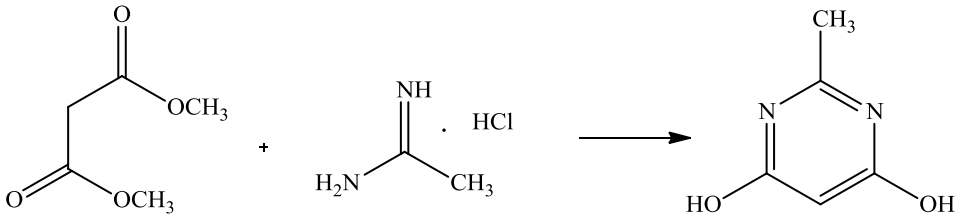


*Fig. 1. Synthesis of MPD.*

This cyclization reaction takes place in an organic alkaline medium and presents significant technological challenges. Due to its strong nucleophilic properties, sodium methoxide ($CH_3ONa$) has been selected as the base, as it enhances substitution at the acyl carbon and promotes ionization, thereby facilitating the reaction [11]. Methanol has been chosen as the solvent due to its higher dielectric constant ($\varepsilon = 33$) compared to ethanol ($\varepsilon = 24$), which improves ion stabilization and increases the efficiency of nucleophilic attack. The reaction is conducted near methanol's boiling point (~50$^o$C), ensuring sufficient thermal energy to drive the process while minimizing excessive solvent evaporation. Under these controlled conditions, an optimal balance is achieved between reaction rate, selectivity, and overall yield.

To further enhance reaction efficiency and maximize yield, a systematic investigation of key technological parameters has been conducted. The study focused on three critical factors: $CH_3ONa$ concentration (14-20 wt%), reaction time (60-240 minutes), and the DEM/Ace·HCl molar ratio (0.8-1.4), all of which significantly influence reaction kinetics, product selectivity, and overall yield. To optimize these conditions while minimizing experimental complexity, the Taguchi method [12] was applied, providing a structured and efficient experimental design approach.

For statistical reliability, three control factors were examined at three levels, and a total of 16 experimental runs were designed using an $L16(4^{3-1})$ orthogonal array. The resulting MPD was characterized using FTIR spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, and melting point determination. Additionally, powder X-ray diffraction (PXRD) analysis was performed, with MPD's PXRD pattern being reported for the first time, offering valuable structural insights into the synthesized compound.

# 2. Experiment

## *2.1. Chemicals*

The chemicals used in this study include acetamidine hydrochloride ($C_2H_6N_2$·HCl, 99%) and diethyl malonate ($C_7H_{12}O_4$, 99%), both sourced from Merck, Germany; absolute methanol ($CH_3OH$) from Fisher Scientific, USA; sodium metal (Na, 99%), hydrochloric acid (HCl, 37%), and calcium hydride powder ($CaH_2$) from Xilong Scientific Co., Ltd., China. The purity of all chemicals was ensured based on supplier specifications, and they were used directly without further purification.

## *2.2. Design of the experiment conditions*

An L16($4^{3-1}$) orthogonal array was utilized to optimize reaction parameters, incorporating three control factors at four levels. These factors included sodium methoxide concentration, reaction time, and the DEM/Ace·HCl molar ratio, each examined at three levels, as detailed in Tab. 1. A full factorial experimental design would necessitate 64 experiments ($N = 4^3$). However, by employing the Taguchi method, the experimental workload was reduced to 16 trials ($N = 4^{3-1}$), as outlined in Tab. 2. Each experiment was performed in duplicate to ensure statistical reliability and to evaluate the signal-to-noise (S/N) ratio.

*Tab. 1. Control factors and levels in the Taguchi experimental design*

| **Control factors** | **Levels** | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| A. Sodium methoxide concentration (%) | 14 | 16 | 18 | 20 |
| B. Reaction time (minutes) | 60 | 120 | 180 | 240 |
| C. DEM/Ace·HCl molar ratio | 0.8 | 1.0 | 1.2 | 1.4 |

## *2.3. Apparatus and procedures for the synthesis of MPD*

Sodium metal is highly reactive and poses significant fire and explosion hazards upon contact with air or water. Appropriate safety measures, including the use of safety goggles, a face shield, and flame-resistant clothing such as a leather lab coat, are required to mitigate risks during handling. All equipment and chemicals exposed to sodium must be thoroughly dried, and prolonged air exposure of sodium should be avoided.

A schematic diagram of the experimental procedure is shown in Fig. 2. For the preparation of dry methanol, the required volume was accurately measured and transferred into a sealable glass beaker. Calcium hydride ($CaH_2$) was added at a ratio of 10-15 g per 1000 mL of methanol, followed by stirring with a glass rod for 3-5 minutes. The beaker was then sealed, and the mixture was allowed to stand for 3-5 hours. The

dried methanol was subsequently decanted into a three-neck flask equipped with a mechanical stirrer and a reflux condenser. Sodium metal was weighed based on stoichiometric calculations to achieve the desired concentration. The sodium was cut into small pieces (5 × 5 mm), flattened using a cylindrical metal roller on filter paper, and gradually added to the dried methanol to generate a sodium methoxide solution.

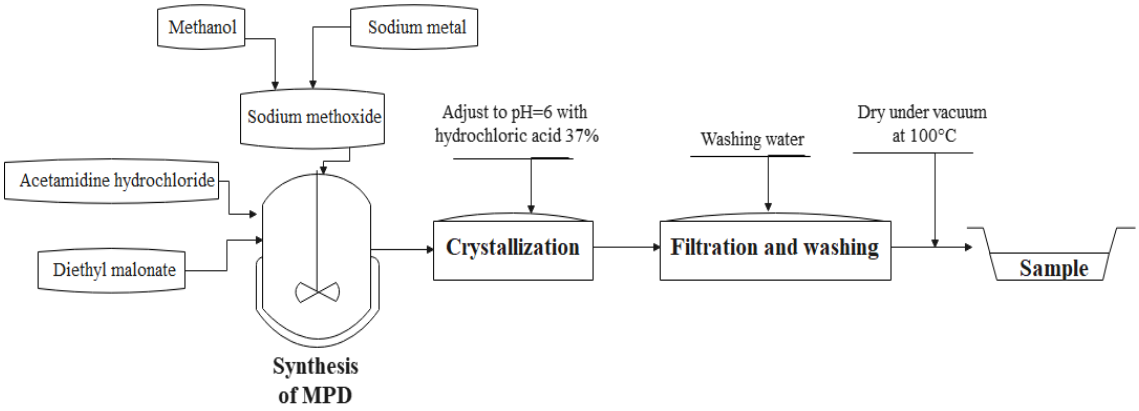


*Fig. 2. Schematic diagram of the experimental procedure.*

A sequential addition of Ace·HCl and DEM was performed into 300 mL of sodium methoxide solution at a predefined concentration. The reaction mixture was maintained at 50°C under continuous stirring at 300-350 rpm. Upon reaction completion, the mixture was cooled to room temperature, and neutralization was conducted using 37% hydrochloric acid until the pH reached 6. Subsequently, 250 mL of distilled water was introduced, followed by stirring for 1 hour. The resulting precipitate was filtered, washed with water, and dried under vacuum at 100°C.

The morphology of the synthesized material was examined using a standard camera and a NIKON YS100 microscope. FTIR spectroscopy (Perkin-Elmer Spectrum 400) was employed to identify functional groups, utilizing a wavenumber range of 400-4000 $cm^{-1}$. Proton nuclear magnetic resonance ($^{1}H$ NMR) and carbon-13 nuclear magnetic resonance ($^{13}C$ NMR) spectra were recorded using a Bruker Avance 600 MHz spectrometer.

The melting point of MPD was determined using an EZ-Melt apparatus. An initial estimation of the melting temperature range was obtained through differential scanning calorimetry (DSC), and the heating temperature was subsequently set within the predicted range, with a controlled heating rate of 5°C/min.

### *2.4. Powder X-ray diffraction*

Powder X-ray diffraction (PXRD) analysis was performed with a Bruker D8 Advance instrument, operating with Copper Kα radiation at a wavelength (λ) of

1.54 nm. The X-ray tube was maintained at 40 kV and 30 mA, and data collection was conducted over a diffraction angle range ($2\theta$) of 10° to 80°, with a step size of 0.01°.

## 3. Results and discussion

### *3.1. Analysis and verification of Taguchi experiments*

The synthesis process of MPD was conducted twice under 16 experimental conditions designed using the Taguchi method, with the average experimental results presented in Tab. 2.

*Tab. 2. Experimental design matrix and experimental results*

| Exp. No. | Control factors | | | Encoded factors | | | Yield of MPD (%) |
|---|---|---|---|---|---|---|---|
| | Sodium methoxide concentration (%) | Reaction time (minutes) | DEM/Ace·HCl molar ratio | x1 | x2 | x3 | |
| T1 | 14 | 60 | 0.8 | 1 | 1 | 1 | 66.2 |
| T2 | 14 | 120 | 1.0 | 1 | 2 | 2 | 74.2 |
| T3 | 14 | 180 | 1.2 | 1 | 3 | 3 | 83.3 |
| T4 | 14 | 240 | 1.4 | 1 | 4 | 4 | 83.8 |
| T5 | 16 | 60 | 1.0 | 2 | 1 | 2 | 77.1 |
| T6 | 16 | 120 | 0.8 | 2 | 2 | 1 | 70.5 |
| T7 | 16 | 180 | 1.4 | 2 | 3 | 4 | 86.3 |
| T8 | 16 | 240 | 1.2 | 2 | 4 | 3 | 85.7 |
| T9 | 18 | 60 | 1.2 | 3 | 1 | 3 | 86.2 |
| T10 | 18 | 120 | 1.4 | 3 | 2 | 4 | 88.0 |
| T11 | 18 | 180 | 0.8 | 3 | 3 | 1 | 76.4 |
| T12 | 18 | 240 | 1.0 | 3 | 4 | 2 | 81.3 |
| T13 | 20 | 60 | 1.4 | 4 | 1 | 4 | 87.3 |
| T14 | 20 | 120 | 1.2 | 4 | 2 | 3 | 87.0 |
| T15 | 20 | 180 | 1.0 | 4 | 3 | 2 | 74.2 |
| T16 | 20 | 240 | 0.8 | 4 | 4 | 1 | 69.3 |

The experimental data were converted into signal-to-noise (S/N) values through Taguchi method analysis. The S/N ratio indicates the impact of noise variables on the desired attributes. In organic compound synthesis studies, synthesis yield is selected as the target characteristic. The obtained yield analysis follows the "larger-is-better" criterion, where a higher value represents a higher yield. Thus, the S/N ratio is calculated using the following formula:

$$\frac{S}{N} = -10\log_{10}\left(\frac{1}{n}\sum_{i=1}^{n}\frac{1}{y_i^2}\right)$$

The results of calculations using Minitab software are shown in Tab. 3, Figs. 3, 4.

*Table 3. Contribution range and ranking of factors to MPD synthesis yield*

| Levels | Control factors | | |
|---|---|---|---|
| | **A. Sodium methoxide concentration (%)** | **B. Reaction time (minutes)** | **C. DEM/Ace·HCl molar ratio** |
| 1 | 76.88 | 79.20 | 70.60 |
| 2 | 79.90 | 79.92 | 76.70 |
| 3 | 82.97 | 80.05 | 85.55 |
| 4 | 79.45 | 80.03 | 86.35 |
| Range | 6.10 | 0.85 | 15.75 |
| Rank | 2 | 3 | 1 |

Table 3 describes the range and significance level of each factor on MPD synthesis yield. The three control factors contribute as follows: 6.10% (A), 0.85% (B), and 15.75% (C). From this, the influence of each control factor on reaction efficiency follows the order C > A > B. The trend of the individual effects of control factors on yield and S/N ratio is illustrated in Figs. 3, 4.

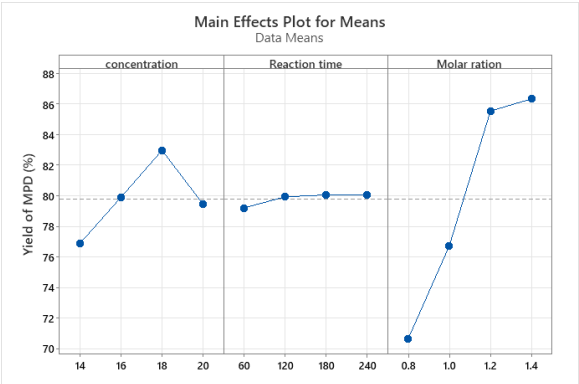


*Fig. 3. The trend of factor influence on MPD synthesis yield.*

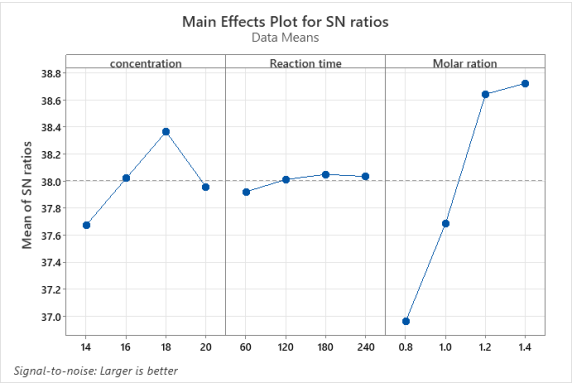


*Fig. 4. The trend of factor influence on S/N ratio.*

The highest yield for each factor was used to determine the optimal conditions, initially identifying A3B3C4 as the most suitable experimental setup. However, for large-scale synthesis, economic factors needed to be considered.

To ensure the accuracy of the Taguchi experimental design, three parallel experiments were conducted under the optimized conditions (A3B3C4). An average

MPD yield of 88.5% was achieved (sample T17), exceeding the results obtained from the 16 experimental sets initially designed using the Taguchi method.

### *3.2. Structure determination of MPD*

The MPD compound is observed as a white powder, with small and uniform crystalline particles under a microscope (Fig. 5). The average particle size is measured to be approximately 5 µm using ImageJ software [13]. The MPD sample synthesized under condition T17 is subjected to melting point determination, followed by characterization through FTIR spectroscopy and NMR spectroscopy. The melting point of MPD is also confirmed.

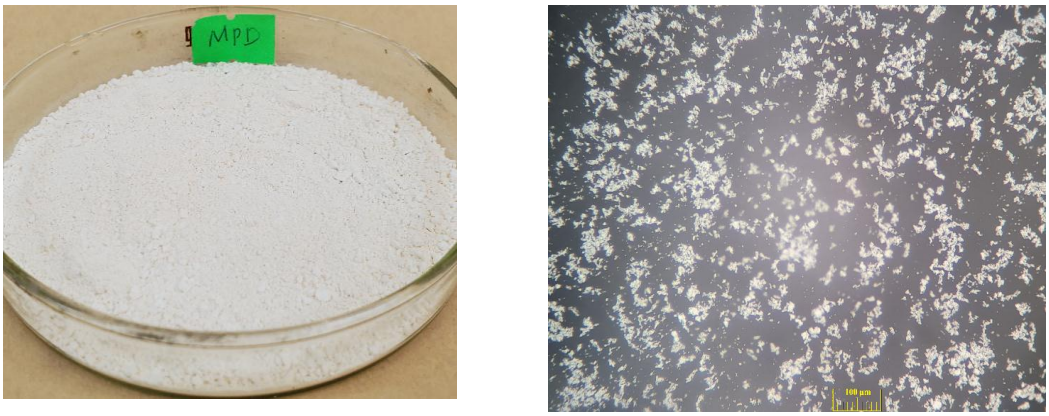


*Fig. 5. Images of the MPD product: (a) as observed with the naked eye and (b) under a microscope at x300 magnification.*

#### *3.2.1. FTIR spectral analysis*

The FTIR spectrum of the solid MPD product (KBr disk) is shown in Fig. 6, with the following peaks observed: 3461 $cm^{-1}$, corresponding to the O-H stretching vibration; 3088 $cm^{-1}$, which may be attributed to the $sp^2$ C-H stretching vibration of the pyrimidine ring; 2800 $cm^{-1}$, potentially associated with the $sp^3$ C-H stretching vibration of the $-CH_3$ group; 1693 $cm^{-1}$ and 1643 $cm^{-1}$, assigned to the C=N stretching vibrations characteristic of the pyrimidine ring; 1578 $cm^{-1}$, which may correspond to C=C bond vibrations within the heterocyclic system; 1219 $cm^{-1}$, possibly indicating C-O stretching vibrations associated with alcohol or phenol-like hydroxyl groups; and the region between 600-900 $cm^{-1}$, where out-of-plane C-H bending vibrations of the pyrimidine ring may be present.

When compared to the infrared spectrum of 4,6-dihydroxy-2-methylpyrimidine reported in the literature [11], [14], consistent functional groups are observed, confirming that the synthesized product is 4,6-dihydroxy-2-methylpyrimidine.

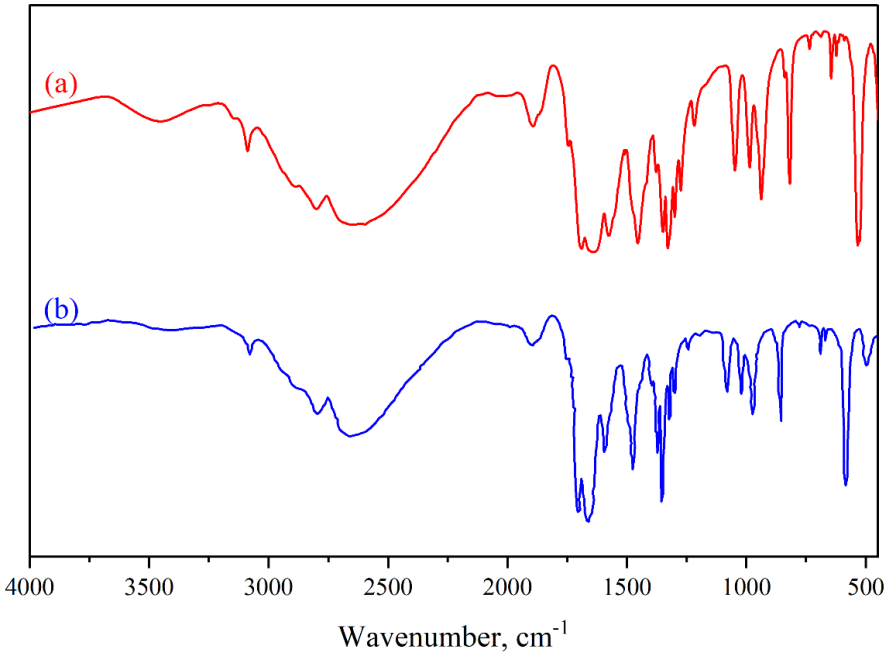


*Fig. 6. FT-IR spectra of the MPD sample: (a) obtained under condition T17 and (b) reference spectrum from* [14].

### *3.2.2. ($^1$H, $^{13}$C)-NMR spectral analysis*

For structural analysis, the synthesized product is dissolved in deuterated dimethyl sulfoxide (DMSO-D6) and examined using nuclear magnetic resonance spectroscopy ($^1$H-NMR, $^{13}$C-NMR). The NMR spectra of the MPD product are shown in Figs. 7, 8.

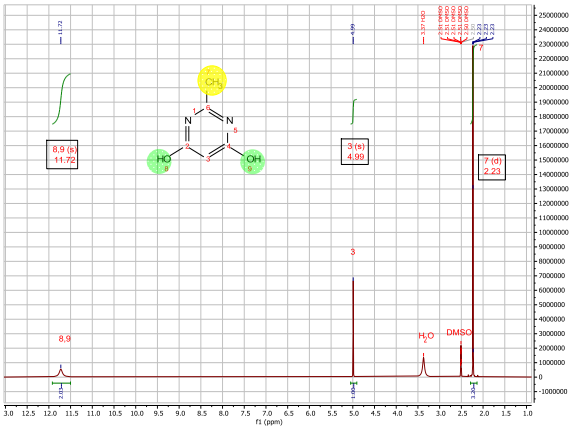


*Fig. 7. $^1$H NMR spectrum of the MPD.*

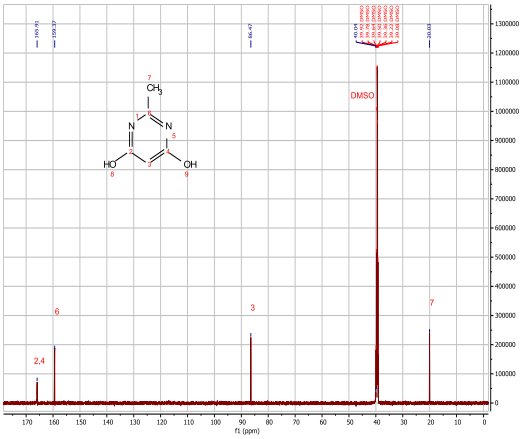


*Fig. 8. $^{13}$C NMR spectrum of the MPD.*

In the $^{1}$H-NMR spectrum (Fig. 7), chemical shifts are observed at δ = 2.23, 4.99, and 11.72 ppm, corresponding to hydrogen atoms in the -$CH_3$, -CH, and -OH positions, respectively. The $^{1}$H-NMR spectrum is in complete agreement with published data [11]. The $^{13}$C-NMR spectrum (Fig. 8) shows chemical shifts at δ = 165.91, 159.37, 86.47, and 20.03 ppm, which are assigned to carbon atoms at positions C(2,4), C(6), C(3), and C(7), respectively. The $^{13}$C-NMR spectrum is in complete agreement with published data [15].

*3.2.3. Melting point determination of MPD*

The melting point of the MPD sample (T17) is presented in Tab. 4. Consistency with reported values from the CAS database [16] was observed. A deviation within ±5°C was noted, which can be attributed to the heating rate of 5°C/min used in the measurement process.

*Tab. 4. Melting point measurement results of the MPD sample*

| **Exp. No.** | **Value (°C)** | **Reference** [16] |
|---|---|---|
| 1 | 365 | 360°C (CAS 40497-30-1) |
| 2 | 360 | |
| 3 | 365 | |
| Mean value | 363.3 | |

### *3.3. Powder X-ray diffraction analysis*

The powder X-ray diffraction (PXRD) patterns of MPD were recorded over a 2$\theta$ range of 10-80° (Tab. 5 and Fig. 9). Tab. 5 presents the PXRD peak values of MPD, which were calculated using X'Pert HighScore Plus software [17]. A total of 18 characteristic diffraction peaks were identified, with the corresponding d-spacing values (d), full width at half maximum (FWHM), and average crystallite size determined using the Scherrer equation.

The positions of the intensity peaks were identified, along with their FWHM and d-spacing values. A reflection peak was observed at 2$\theta$ = 27.24°, corresponding to a d-spacing value of 32.71 nm and a grain size of 23.14 nm.

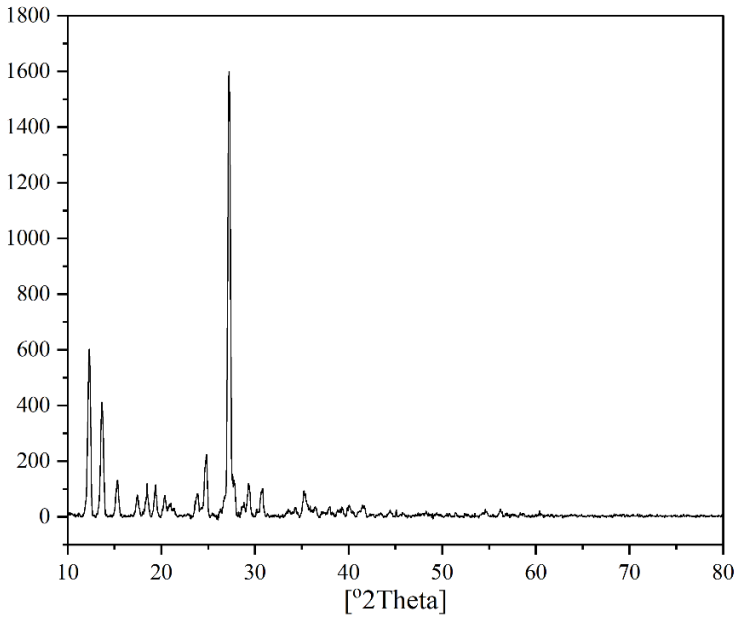


*Fig. 9. PXRD pattern of MPD.*

*Tab. 5. PXRD data of the MPD*

| No. | Angle in 2$\theta$ | *d* value in nm | FWHM | Grain size in nm |
|---|---|---|---|---|
| 1 | 12.30 | 71.92 | 0.335 | 23.85 |
| 2 | 13.67 | 64.74 | 0.345 | 23.20 |
| 3 | 15.29 | 57.89 | 0.327 | 24.54 |
| 4 | 17.44 | 50.80 | 0.318 | 25.27 |
| 5 | 18.47 | 47.99 | 0.311 | 25.86 |
| 6 | 19.37 | 45.78 | 0.289 | 27.91 |
| 7 | 20.62 | 43.04 | 1.002 | 8.06 |
| 8 | 23.84 | 37.30 | 0.442 | 18.38 |
| 9 | 24.76 | 35.93 | 0.332 | 24.51 |
| 10 | 27.24 | 32.71 | 0.316 | 25.88 |
| 11 | 29.34 | 30.42 | 0.347 | 23.69 |
| 12 | 30.74 | 29.07 | 0.334 | 24.66 |
| 13 | 35.35 | 25.37 | 0.537 | 15.54 |
| 14 | 37.94 | 23.69 | 0.331 | 25.41 |
| 15 | 40.07 | 22.48 | 0.422 | 20.03 |
| 16 | 41.51 | 21.74 | 0.494 | 17.19 |
| 17 | 54.62 | 16.79 | 0.355 | 25.19 |
| 18 | 56.21 | 16.35 | 0.242 | 37.29 |

## 4. Conclusion

In this study, the Taguchi experimental design method was utilized to determine the optimal reaction conditions for the condensation of Ace·HCl and DEM in a sodium methoxide medium for MPD synthesis. The reaction temperature was maintained at 50°C, and the optimal synthesis parameters were identified as follows: sodium methoxide concentration of 18%, reaction time of 180 minutes, and a DEM/Ace·HCl molar ratio of 1.4, resulting in a maximum MPD yield of 88.5%.

To characterize MPD, several advanced analytical techniques were applied, including FTIR spectroscopy, NMR spectroscopy, and melting point determination. The results confirmed that the synthesized product was MPD. Additionally, for the first time, PXRD data for MPD were reported in this study.

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# NGHIÊN CỨU TỐI ƯU HOÁ QUY TRÌNH TỔNG HỢP VÀ MỘT SỐ TÍNH CHẤT CỦA 4,6-DIHYDROXY-2-METHYL PYRIMIDINE

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**Tóm tắt:** 4,6-dihydroxy-2-methylpyrimidine (MPD) là một tiền chất quan trọng trong ngành dược phẩm và tổng hợp các hợp chất hữu cơ, đồng thời gần đây đã thu hút sự quan tâm như một chất trung gian triển vọng trong quy trình sản xuất vật liệu năng lượng cao giảm nhạy FOX-7. Một phương pháp tổng hợp hiện đại dựa trên phản ứng ngưng tụ giữa acetamidine hydrochloride ($C_2H_6N_2$·HCl) và diethyl malonate ($C_7H_{12}O_4$) trong môi trường kiềm hữu cơ. Tuy nhiên, các dữ liệu liên quan đến thông số công nghệ ảnh hưởng đến hiệu suất phản ứng vẫn còn hạn chế. Trong nghiên cứu này, phương pháp thiết kế thí nghiệm Taguchi đã được áp dụng nhằm tối ưu hóa điều kiện phản ứng để nâng cao hiệu suất tổng hợp MPD. Kết quả từ các thí nghiệm xác nhận cho thấy các điều kiện tối ưu bao gồm: nồng độ natri methoxide 18%, thời gian phản ứng 180 phút, và tỉ lệ mol DEM/Ace·HCl là 1,4. Trong điều kiện này, hiệu suất tổng hợp MPD đạt tối đa 88,5%. Sản phẩm MPD thu được đã được định danh thông qua các kỹ thuật phổ như: cộng hưởng từ hạt nhân (NMR), hồng ngoại (FTIR) và điểm nóng chảy. Đặc biệt, phân tích nhiễu xạ bột tia X (PXRD) cũng lần đầu tiên được xác định và công bố.

***Từ khóa:*** *4,6-dihydroxy-2-methylpyrimidine; tối ưu hoá; phương pháp Taguchi; FOX-7.*

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