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Article

Scale-Up of a Continuous Manufacturing Process of Edaravone

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ABSTRACT: Edaravone belongs to a class of brain-protective agents, which can scavenge free radicals. To reduce impurities and improve the yield, a continuous flow production process of edaravone was developed. The synthesis is continuously carried out in two steps. The throughput can reach 11.328 kg/day and the purity of the final product is 99.95%, which are in accordance with the needs of production. This is an efficient and quick production process suitable for industrial production.

KEYWORDS: *edaravone, free radical scavenger, continuous flow, scale-up synthesis, industrial process*

1. INTRODUCTION

Edaravone (3-methyl-1-phenyl-2-pyrazoline-5-one, CAS No. 89-25-8) is an antioxidant, which is considered as a free radical scavenger. It has been reported that it can eliminate lipid peroxides and hydroxyl radicals. Edaravone was developed by Mitsubishi Tanabe Pharma Corporation and was approved to improve neurological symptoms, activities of daily living, and dysfunction caused by acute cerebral infarction in Japan, in 2001.[1−5] In 2017, the US Food and Drug Administration approved edaravone for the treatment of patients with amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease.[6−10] Therefore, the demand for edaravone is increasing in the current market.

The general synthesis method is that ethyl acetoacetate (**1**) and phenylhydrazine (**2**) are refluxed in ethanol and the crude edaravone used in the industry at present is obtained (Scheme 1). Its disadvantages are low yield, complex purification process, and the presence of many impurities.[11−14] Recrystallization is the main method to improve the purity, but this leads to a low yield.[15−17] In fact, when **1** and **2** were refluxed in ethanol to obtain a 100 g scale product in batch experiments in our laboratories, the result showed that there were many impurities, including the impurities **3**, **4**, **5**, and **6** reported in the literature, as shown in Scheme 1.[18,19] The conversion rate is low, and the product content in the reaction solution is only 82.1%. Although the crude product can be recrystallized to greatly improve its purity, the contents of residual impurities were still high, which would directly lead to a lower yield.

In recent years, it has also been reported that edaravone was synthesized by microwave and ultrasonic methods, with a high yield and few impurities.[20−22] However, these technologies are not suitable for expanding the production process. It has also been reported that edaravone is synthesized by continuous flow technology, but it is only synthesized on a gram scale and needs high temperature and chromatographic separation, which was not a suitable industrial process.[23] In view of the unique advantages of continuous flow, such as a smaller pore size, larger contact area, and higher heat transfer efficiency, this method is more suitable for modern industrial production than batch experiments.[24−27] Meanwhile, compared with the batch process, continuous flow minimizes the decomposition of phenylhydrazine by reducing exposure to moisture, oxygen, and light during the reaction, which is beneficial to improve the purity and yield.

A new synthesis method of edaravone is reported here, which adopts continuous flow, two-step continuous reaction, and one-time recrystallization. The purity of the product is 99.95%, and the yield is 88.4%. This method is suitable for industrial production.

2. RESULTS AND DISCUSSION

In the preliminary experiments, ethanol was used as the solvent to dissolve **1** and **2**. Two plunger pumps were used to introduce them into the device separately. After being mixed in a T-shaped mixer, they reacted in a microreactor and flowed out through a back pressure regulator (BPR); the reaction solution was finally obtained (Figure 1).

The results indicated that the target product edaravone was not obtained, but intermediate **7** was formed. After optimizing the reaction temperature, residence time, pressure, and other conditions, this was somewhat unexpected, but most of intermediate **7** was still obtained (Table 1, entries 1−4). Finally, edaravone was mainly obtained at a high temperature (Table 1, entries 5−6). However, when the temperature was 100 °C, the content of edaravone was only 76.9%, the content of intermediate **7** was 10.1%, and many impurities were produced (Figure 2, see the Supporting Information for more information), which was worse than batch experiments. This meant that more impurities would be produced in a higher temperature environment.

This led to a contradiction, that is, a higher temperature was needed to promote the completion of the reaction, but more

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Scheme 1. Conventional Batch Synthesis Route and Impurities of Edaravone

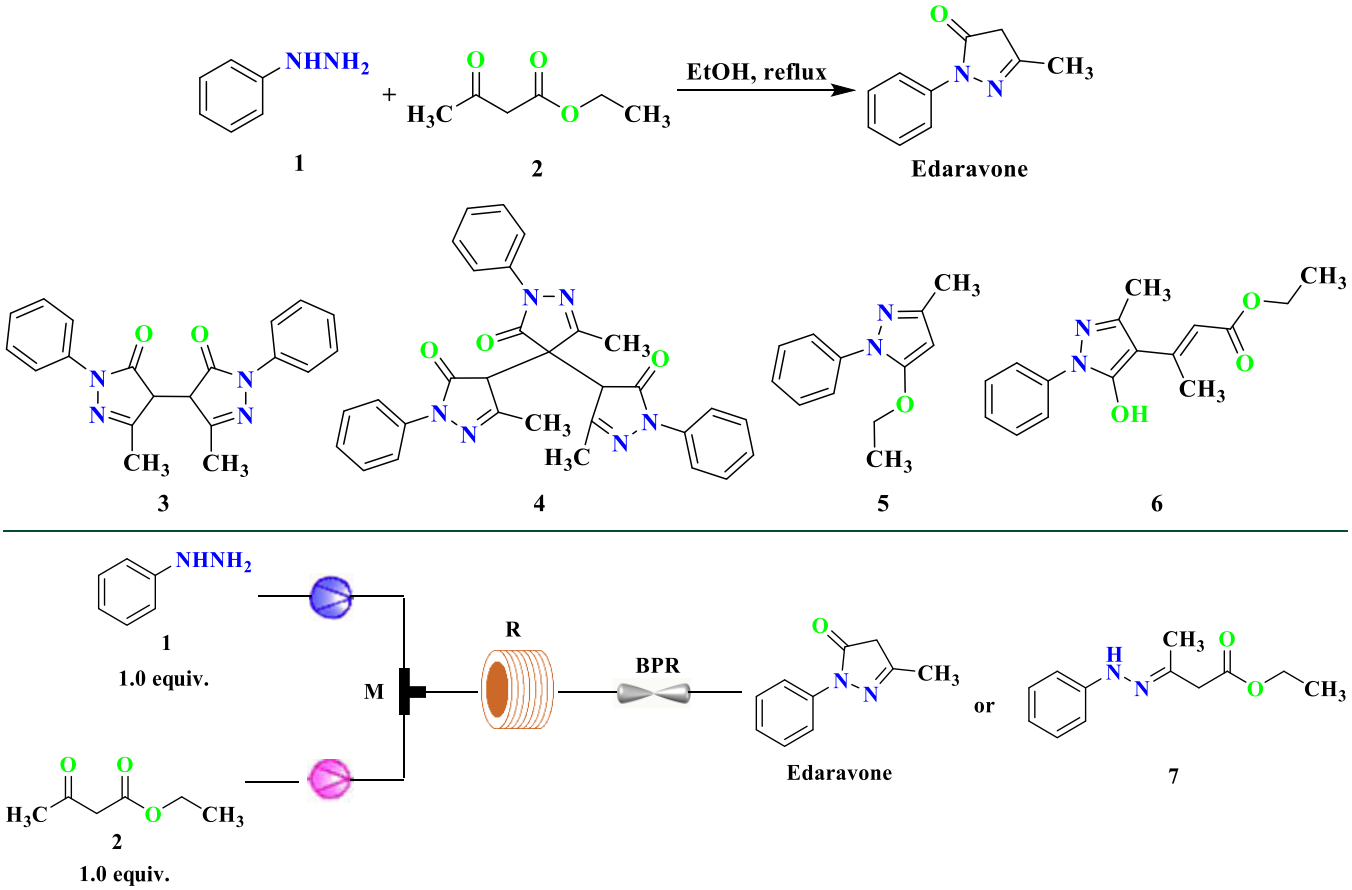

Figure 1. First flow chemistry diagram of the synthesis of edaravone.

Table 1. Optimization of Flow Synthesis of Edaravone

entry	solvent	residence time (min)	temperature (°C)	pressure (MPa)	edaravone (%)[a]	7 (%)[a]
1	ethanol	5	60	0	0	85.2
2	ethanol	5	70	0	0	85.3
3	ethanol	5	80	0.4	0	82.5
4	ethanol	5	90	0.9	43.8	33.6
5	ethanol	5	100	1.3	75.2	8.6
6	ethanol	3	100	1.3	76.9	10.1
7	toluene	3	100	0.6	78.0	2.5
8	1,4-dioxane	3	100	1	78.3	1.8
9	glycol	3	100	0.7	80.3	5.7
10	ethanol	0.5	25	0	0	99.1

[a]Tested by HPLC.

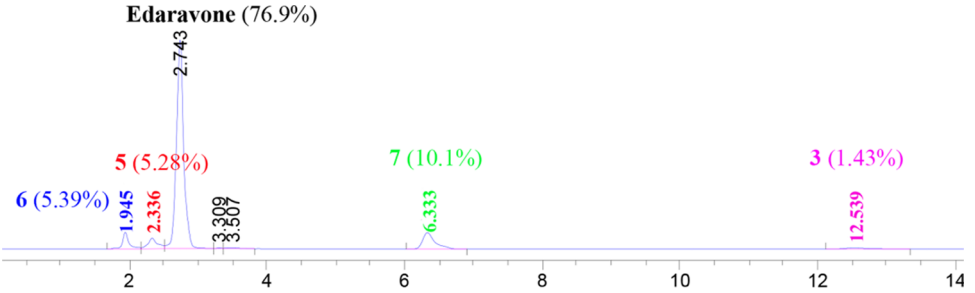

Figure 2. HPLC spectrum of the reaction solution at 100 °C in ethanol (Table 1, entry 6).

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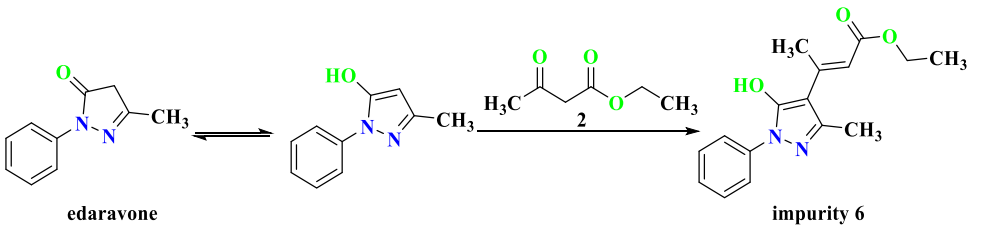
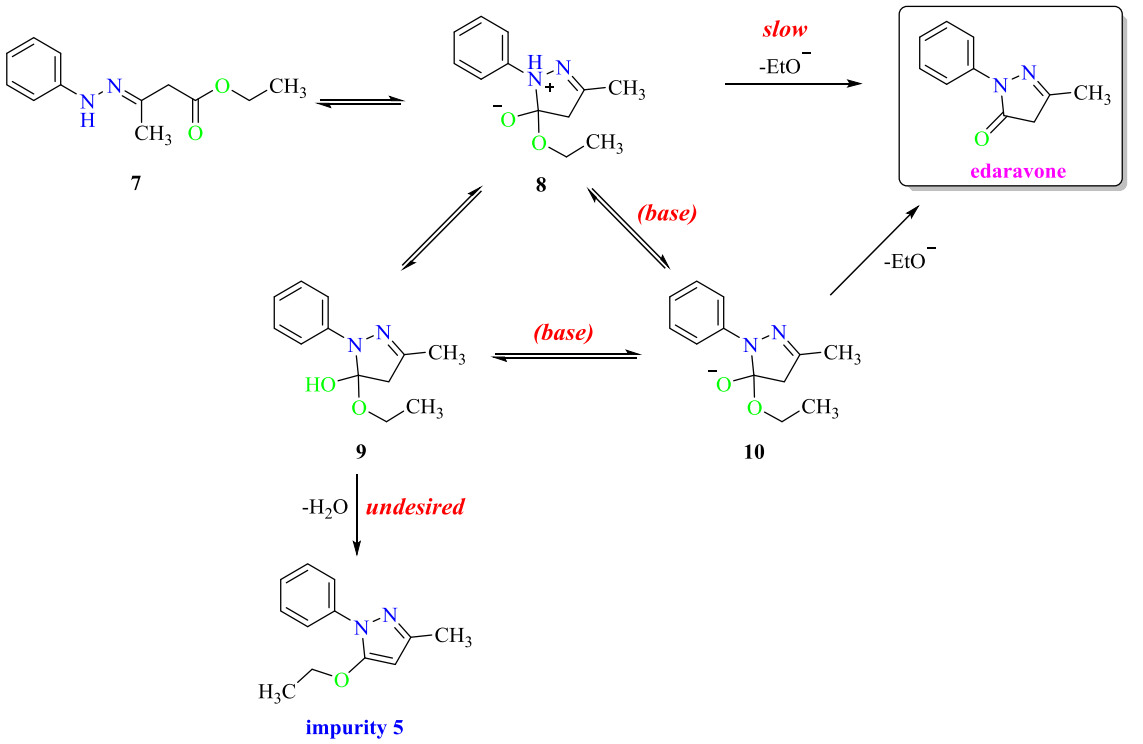
Scheme 2. Generation of Impurity 6



Scheme 3. Possible Reaction Mechanism



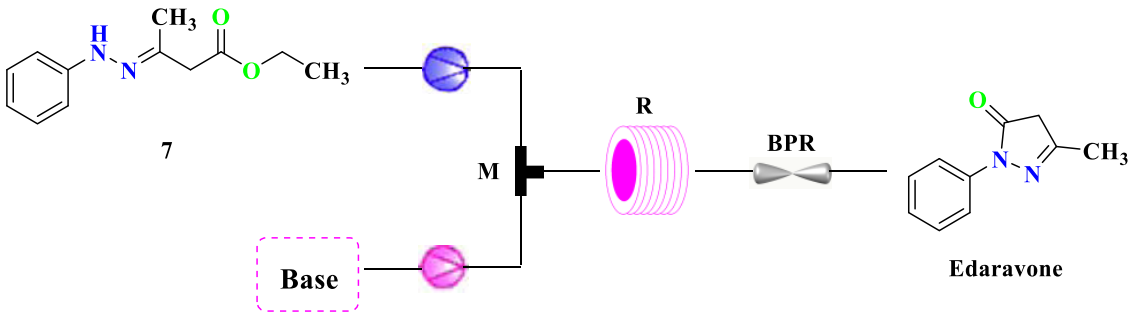


Figure 3. Flow chemistry diagram of the synthesis of step 2.

impurities were produced. To reduce the formation of impurities, ethanol was replaced by other solvents, but the same results were obtained (Table 1, entries 7−9). Considering the recrystallization in the purification process, ethanol was the best solvent choice, so other methods should be developed to improve the yield and purity at a relatively low temperature, while ethanol is still the solvent conducive to industrial production.

Interestingly, in previous experiments, intermediate 7 was obtained under mild conditions with high purity and high yield (Table 1, entry 10). Based on this result, we developed a new process, that is, the synthesis of edaravone was divided into two steps. The intermediate 7 was prepared in the first step, and then the edaravone was prepared by a cyclization reaction in the second step. This operation has two main advantages. The first step can be carried out under mild conditions to avoid the deterioration of phenylhydrazine. It can also avoid the production of impurity **6**, which was more likely to be produced in one-pot experiments (Scheme 2). The intermediate 7 can be obtained with high yield through a rapid reaction, as in the previous experiment, and the second cyclization reaction would be systematically studied in the follow-up study to obtain the edaravone based on the intermediate 7.

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After analyzing the possible reaction mechanism of the cyclization reaction according to relevant literature (Scheme 3), it is necessary to add a base to make the reaction easy to complete, so that ethanol can be used as a solvent at last.[28−33] The mechanism involves the nucleophilic attack of the amine at the carbonyl group, followed by the expulsion of the alkoxy group from the tetrahedral intermediate. The tetrahedral intermediate formed in aminolysis can exist in several forms that differ in the extent and the site of protonation, such as intermediate **8**−**10**. The direct production of edaravone from intermediate **8** is very slow due to the poor ability of the leaving ethoxy anion in intermediate **8**, and the edaravone is produced more from intermediate **10**. When a base is used, intermediate **8** would quickly transfer to the more stable intermediate **10**, so the reaction rate would be faster than before, even at a lower temperature. Finally, the intermediate **10** quantitatively produces edaravone. It should be noted that when a base is used, the impurity **5** could also be avoided because the formation of intermediate **10** is rapid, and the undesired elimination is suppressed.

To investigate the cyclization reaction, the intermediate **7** and different types of bases were introduced into the microreactor (Figure 3). K_2CO_3, NaOH, CH_3ONa, C_2H_5ONa, and Et_3N were chosen as bases to test the reaction conditions (Table 2). As stated in the mechanism, all of the

Table 2. Investigation of Step 2

entry	base	equiv of base	temperature (°C)	residence time (min)	yield (%)[a]
1	NaOH	1	80	2	46.5
2	NaOH	1.5	80	2	67.2
3	NaOH	2	80	2	88.9
4	NaOH	2	50	2	90.2
5	NaOH	2	30	2	92.5
6	NaOH	2	20	2	93.3
7	NaOH	1	20	2	51.6
8	K_2CO_3	2	20	2	92.1
9	CH_3ONa	2	20	2	92.0
10	CH_3CH_2ONa	2	20	2	91.7
11	Et_3N	2	20	2	91.5

[a]Tested by HPLC.

five selected bases can make the reaction proceed rapidly, even at room temperature. But 2 equiv of the base was needed to complete the reaction, which may be due to the presence of keto−enol tautomerism in edaravone. After further comparison, the CH_3ONa and C_2H_5ONa are not very good choices because they needed more ethanol to dissolve, which might lead to a lower crystallization yield compared to the inorganic base. Et_3N had the same problem, and it was not easy to be removed completely compared with other bases. As for K_2CO_3 and NaOH, the prices and the reaction results of the two were similar. However, due to the larger molecular weight compared with NaOH, a constant equivalent of K_2CO_3 needs more water to dissolve, which would reduce the solubility of edaravone in the mixed solvent. Therefore, NaOH was finally selected as the base, which needed a small amount of water.

The specific reaction conditions were optimized, including concentration, residence time, and reaction temperature (Table 3). As we all know, in industrial production, high concentration and low solvent consumption are economic and environmentally friendly. Therefore, on the premise of the

Table 3. Optimization of Step 2

entry	concentration of 7 (mol/L)	residence time (min)	temperature (°C)	yield (%)[a]
1	0.5	2	25	88.5
2	1.0	2	25	87.2
3	2.0	2	25	
4	2.0	2	50	89.2
5	3.5	2	50	90.3
6	4.2	2	50	
7	4.2	2	70	
8	3.84	1	50	88.1
9	3.84	1	60	94.5
10	3.84	1	70	90.3

[a]Tested by HPLC.

completion of the reaction, the concentration of raw materials should be as high as possible, so as to improve reaction efficiency. However, there was a problem that the solubility of the product edaravone in ethanol−water solution was not high because sodium hydroxide is an aqueous solution, and the intermediate **7** was an ethanol solution. The results showed that when the concentration of intermediate **7** was 2 mol/L and the temperature was 25 °C, edaravone solid will precipitate and block the microreactor tube because edaravone reached saturation and some product precipitate as a solid in this condition (Table 3, entry 3). Then, the reaction temperature was appropriately increased to improve its solubility. However, it was not suitable for intermediate **7** with a high concentration, such as 4.2 mol/L (Table 3, entries 6 and 7). At last, when the concentration of intermediate **7** was 3.84 mol/L, the temperature was 60 °C and the residence time was 1 min; the reaction could proceed smoothly without solid precipitation. The purity of the edaravone in the reaction solution was determined to be 94.5% by HPLC.

The last problem was the crystallization of edaravone after the optimal reaction conditions had been selected. The solvent was ethanol−water, which was suitable for crystallization. However, edaravone did not precipitate even when the solution cooled. Considering that the pH value could be an important factor, the pH value was adjusted to 7 with hydrochloric acid at 0 °C and precipitation occurred. It was an interesting result, but the ratio of ethanol to water was required to be optimized so that the largest amount of precipitation could be obtained. Since the amount of ethanol had been determined in the previous study, here the focus was on the amount of water. The concentrations of sodium hydroxide and hydrochloric acid were systematically studied based on the same concentration of intermediate **7**, 3.84 mol/L (Table 4). When the concentration of sodium hydroxide was too low, it

Table 4. Investigation of Crystallization

entry	c (NaOH) (mol/L)	c (HCl) (mol/L)	ratio ($EtOH/H_2O$)	yield (%)[a]
1	3.84		0.36:1	
2	7.68		0.59:1	
3	11.52	6	1.8:1	78.8
4	15.36	6	2.8:1	90.2
5	23.04	6	5.7:1	53.5
6	15.36	4	2.4:1	68.0
7	15.36	8	3.2:1	85.1

[a]Calculated based on product weight.

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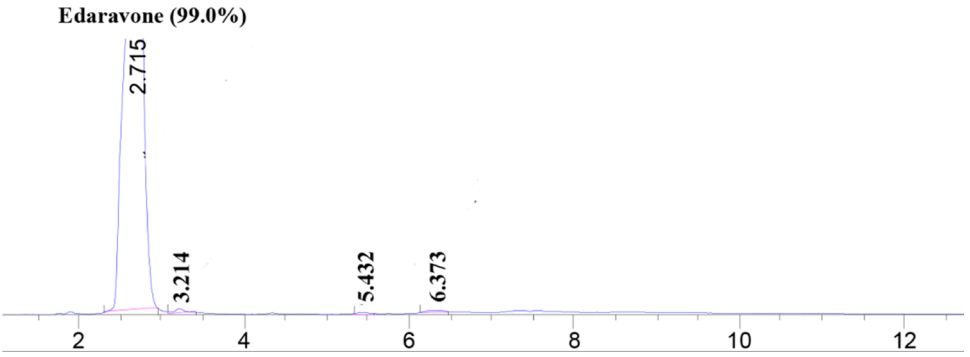

Figure 4. HPLC spectrum of solid (Table 4, entry 4).

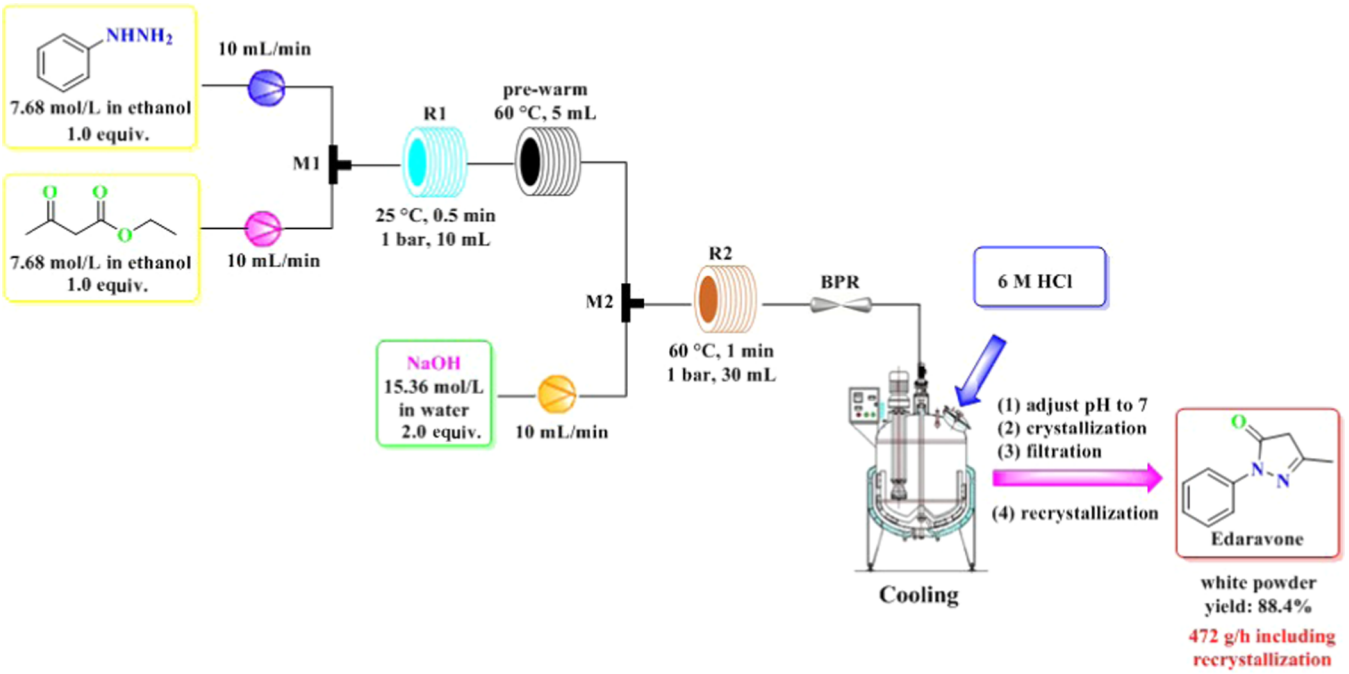

Figure 5. Final continuous flow diagram of the synthesis of edaravone.

Table 5. Comparison among Three Methods for Synthesis of Edaravone

entry	reaction time	product[d](g)	yield (%)	purity[e] (%)	PMI[f]	productivity (kg/day)	STY[g] (kg/(dm^3 day)
1[a]	6 h	59.5	74.2	96.04	10.8	0.238	0.1194
2[b]	4 h	68.1	85.0	98.92	8.96	0.409	0.2854
3[c]	6 min	70.8	88.4	99.95	8.62	11.328	16.99

[a]Traditional method in batch. [b]New method in batch. [c]New method in a continual flow. [d]Amount of product after recrystallization. [e]Tested after recrystallization. [f]Including recrystallization. [g]Calculated based on the reactor internal volume.

meant that too much water led to blockages of pipeline or low crystallization yield (Table 4, entries 1−3), and when it was too high, the strong alkaline environment led to reduced yield (Table 4, entry 5). The highest yield (90.2%) after crystallization was obtained when using 15.36 mol/L NaOH and 6 mol/L HCl, and the ratio of ethanol to water was 2.8:1 (Table 4, entry 4). The assay of edaravone in the solid was 99.0% by HPLC before recrystallization, and there were few impurities (Figure 4). It should be noted that impurities **3**, **4**, **5**, and **6** were not observed due to this continuous flow process, and there were only three impurities, which could be minimized to below 0.1% by conventional recrystallization.

After completing the above research, the two-step flow reactions were connected to a continuous device in sequence (Figure 5). First, phenylhydrazine (7.68 mol/L in ethanol) and ethyl acetoacetate (7.68 mol/L in ethanol) were introduced into the microreactor R1 (25 °C, 0.5 min, 1 bar) by two plunger pumps separately, and the flow rates were both 10 mL/min. Then, the solution flowed into the microreactor R2 after passing through a prewarm device for keeping the solution at 60 °C. At the same time, sodium hydroxide (15.36 mol/L in water) was introduced into the microreactor R2 (60 °C, 1 min, 1 bar) by a plunger pump (10 mL/min) and the second step of cyclization reaction was completed. Finally, crude edaravone was obtained after the solution that flowed from R2 was adjusted to neutrality with 6 M HCl and filtered. Then, recrystallization was carried out once with ethanol−water to obtain pure edaravone. To test the robustness of the

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setup, 708 g of pure edaravone was obtained after 1 h of continuous operation, with a yield of 88.4% and a purity of 99.95% after undergoing recrystallization once. The current flow method has been proved to be a convenient and rapid method, and because of its stability compared to the batch process, it can better produce edaravone on a large scale.

To compare the differences among three methods for synthesis of edaravone (traditional method in batch, new method in batch, and new method in continuous flow), three corresponding experiments were carried out with the same amount of raw materials (phenylhydrazine 50 g, 0.46 mol; ethyl acetoacetate 60.2 g, 0.46 mol), which greatly showed the advantages of continuous flow (Table 5). The results showed that the yields of the new method (85.0 and 88.4%) were higher than that of the traditional method (74.2%), which indicated the significance of the base. Although the yields of the two new methods were similar in batch or flow, the purity is quite different even if the same recrystallization processes were carried out. The purity of this batch was 98.92%, and the content of four impurities exceeded 0.1%, which does not meet the requirements of pharmacopeia. The purity of continuous flow was 99.95%, and the content of one impurity was only 0.05%. Therefore, when the same new methods were used, the continuous flow process had higher purity and shorter operation time compared to the batch process, which was more advantageous in the industry. To further demonstrate the high efficiency and time-saving characteristic of continuous flow, productivity and space−time yield (STY) were estimated. Thanks to these continuous flow process improvements, the productivity and STY of the whole process were greatly improved in the manufacturing scale.

3. CONCLUSIONS

A new production process for the edaravone using continuous flow has been developed, which can reduce the impurities and increase the yield. The synthesis was carried out in two steps continuously. In the second step, it was easier to promote the reaction with sodium hydroxide. The pH was set to make the product directly precipitate out to obtain white solid after the outflow. Compared with batch experiments, this process was more effective and faster and was more suitable for industrial production. In addition, the flow process was demonstrated stably with a productivity of 11.328 kg/day.

4. EXPERIMENTAL SECTION

4.1. General Information. All chemicals and solvents were purchased from commercial suppliers, and they were used without further purification. Mass spectra were obtained on an Agilent 1100 series LC/MSD Tarp (SL). The ^{1}H NMR spectrum was recorded on a Bruker AV-400 spectrometer, and TMS was used as the internal standard. Product purities were determined by HPLC conducted on an Agilent 1100 system using a reverse-phase C18 column (4.6 mm in inside diameter and 25 cm in length), and MeOH-H_2O was used as the mobile phase; the wavelength was 240 nm. The samples were dissolved in methanol to prepare a solution of 1 mg/mL and injected with 20 μL for determination. Continuous flow instruments include a microreactor (with an inner diameter of 0.76 mm, channel length of 10−70 m, pipe material of Hastelloy C276), plunger pumps (Hastelloy C276), and a high and low temperature circulation device (Oushisheng (Beijing) Technology Co., Ltd.).

4.2. Traditional Method in Batch. Phenylhydrazine (50 g, 0.46 mol) was added to ethyl acetoacetate (60.2 g, 0.46 mol) in ethanol (600 mL) at room temperature. The reaction mixture was heated at reflux for 5 h and then cooled, filtered, and recrystallized from ethanol−water to afford target compounds edaravone 59.7 g, yield 74.2%. The purity was 96.04%.

4.3. New Method in Batch. Phenylhydrazine (50 g, 0.46 mol) was added to ethyl acetoacetate (60.2 g, 0.46 mol) in ethanol (240 mL) at room temperature, and the mixture was stirred for 1 h. Then, NaOH (60 mL, 15.36 mol/L) was added slowly. The reaction mixture was heated at 60 °C for 2 h and then cooled down to 0 °C. Then, the pH was adjusted to 7 with HCl (6 M), filtered, and recrystallized from ethanol−water to afford the target compound edaravone 68.5 g, yield 85.0%. The purity was 98.92%.

4.4. New Method in a Continuous Flow Process in 1 h. As shown in Figure 5, two plunger pumps were separately used to introduce phenylhydrazine (7.68 mol/L in ethanol) and ethyl acetoacetate (7.68 mol/L in ethanol) into the microreactor R1 (25 °C, 0.5 min, 1 bar); the flow rates were both 10 mL/min. Then, the solution flowed into the microreactor R2 after passing through the prewarm device, which was used to keep the solution at 60 °C. At the same time, NaOH (15.36 mol/L in water) was introduced by a plunger pump (10 mL/min) into the microreactor R2 (60 °C, 1 min, 1 bar). The resulting mixture was collected in a container for 1 h and cooled down to 0 °C after passing through a back pressure regulator (1 bar). Solids precipitated when the pH was adjusted to 7 with 6 M HCl and filtered (736 g of crude product was obtained; crude yield 92.0%). Then, pure edaravone was obtained after recrystallizing from ethanol−water as white solid (708 g, total yield 88.4%). The purity was 99.95%. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.98−7.78 (m, 2H), 7.47−7.33 (m, 2H), 7.22−7.15 (m, 1H), 3.42 (s, 2H), 2.19 (s, 3H). MS m/z: 175.09 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00228.

Mass spectrum of intermediate 7; HPLC spectrum of intermediate 7; mass spectrum of edaravone; ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of edaravone; HPLC spectrum of the reaction solution at 100 °C in ethanol (Table 1, entry 6); HPLC spectrum of edaravone from the new method in a continual flow process before crystallization; HPLC spectrum of edaravone from the new method in a continual flow process after crystallization; HPLC spectrum of edaravone from the new method in a continual flow process after recrystallization; HPLC spectrum of edaravone from the traditional method in batch; HPLC spectrum of edaravone from the new method in batch; and calculations of productivity, space−time yield (STY) and process mass intensity (PMI) (PDF)

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Notes

The authors declare no competing financial interest.

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