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Research Article

Microwave-Assisted Synthesis of Isopropyl β-(3,4-Dihydroxyphenyl)-α-hydroxypropanoate

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Using microwave irradiation heating, isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate was synthesised from 3,4-dihydroxybenzaldehyde and acetylglycine through the formation of 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones, α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid, and β-(3,4-dihydroxyphenyl)pyruvic acid followed by Clemmensen reduction and esterification. The reaction conditions in terms of operating parameters were optimised by using an orthogonal design of experiment (ODOE) approach, including reaction temperature, reaction time, and microwave power level. Compared with conventional heating, the reaction time was significantly reduced for all reactions and the product yields were increased (except for the third-step reaction) under microwave heating conditions. The most remarkable microwave enhancement was found in the step of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate production where the reaction time was reduced from 10 hrs (conventional heating) to 25 mins (microwave heating) whilst the yield was increased from 75.6% to 87.1%, respectively.

1. Introduction

Recent studies have demonstrated the pharmaceutical activity of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate against cerebral ischemia and hypobaric hypoxia of high altitude [1–4]. As a result, chemical synthesis of this compound and its derivatives has been of great interest. The most commonly used method for synthesising this compound involved the preparation of 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones, α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid, and β-(3,4-dihydroxyphenyl)pyruvic acid which was reduced via Clemmensen reaction that was followed by final esterification [2, 5] under the conventional heating conditions. Other synthesis routes were also explored, for example, by taking steps of benzyl protection, Darzens reaction, selective ring opening by Lewis acid, reduction, and, finally, catalytic hydrogenation [4]. However, those methods suffered from low yield, poor reproducibility, and a long reaction time.

Owing to its advantages over the conventional heating method, microwave heating has been applied to a wide range of organic synthesis processes [6–9], following the pioneering work by Gedye et al. [10] and Giguere et al. [11] in the 1980s. The main advantages include the acceleration of reaction rate [12–14], improved product selectivity [15–18], and high yield [18–20]. The application of microwave heating has also been explored in the field of organic synthesis for drug discovery [21, 22]. In our previous study, we employed a microwave heating method for the synthesis of Danshensu, which is an active compound/ingredient in a traditional Chinese herbal medicine Danshen (Salvia miltiorrhiza); we observed improved yields with shorter reaction time compared with conventional heating [23]. For the optimisation of experimental conditions, design of experiments (DOE) has been used as a powerful approach to reduce the variation in a process and, ultimately, to produce high quality product at low cost for manufacturing [24, 25]. Among various DOE

approaches, the Taguchi method [26] has been frequently employed to investigate the effect of different parameters on the mean and variance of a process performance characteristics which defines how well the process is functioning; it generally involves using orthogonal arrays to organise the parameters affecting the process and the levels at which they should be varied [25, 27].

In the present study, we extended the microwave-assisted method to the synthesis of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate (Scheme 1). A design of experiments via Taguchi method was used to determine the influencing factors and levels in order to optimise the product yield; the factors included reaction temperature, reaction time, and microwave power level.

2. Results and Discussion

2.1. Selection of Operating Reaction Parameters. The main focus of this study was to investigate the effect of microwave radiation heating on the four-step synthesis process in comparison to conventional heating method. The reaction conditions were initially examined by varying reaction temperature, reaction time, and microwave radiation input power level in order to determine the variable range. Based on the initial results, an orthogonal experimental design was carried out, and the three experimental factors at three levels for each synthesis step are shown in Table 1.

2.2. Synthesis of 2-Methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones. With the determination of experimental factors and levels shown in Table 1 experiments were carried out following the orthogonal test programs, $L_9(3^3)$. The experimental results are summarised in Table 2. All yields shown in the tables are the mean value of three experiment runs. The experimental data was analysed with statistical software Minitab 16, and the ANOVA results are shown in Table 3.

The variance analysis showed that all three factors had insignificant impact on reaction yields at the selected level ranges as all three P values were greater than 0.05. However, the order of influencing factors was C > B > A, indicating that the microwave radiant power was the dominant influence among the three. The highest yield of 89.7% was obtained under the conditions of $A_2B_2C_3$ among the nine experiment runs. The design of experiment suggested the optimised conditions of $A_2B_2C_2$, and using that optimisation a yield of 90.8% was obtained in the experiment. That confirmed the optimised reaction conditions of $A_2B_2C_2$ for the microwave synthesis of 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones.

2.3. Synthesis of α-Acetylamino-β-(3,4-diacetoxyphenyl)acrylic Acid. Table 4 shows the orthogonal test programs, $L_9(3^3)$, and test results for the synthesis of α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid under microwave heating conditions. The ANOVA results are shown in Table 5.

The variance analysis also showed that all three factors had no significant impact on reaction yields at the selected level ranges where all three P values were greater than 0.05. However, the order of influencing factors was found to be C > B > A, suggesting that the microwave radiant power was the dominant influence among the three. The best experiment result (i.e., yield 87.5%) from the nine experimental runs was obtained under the reaction of $A_1B_3C_3$. The optimum conditions found from the design of experiment were $A_2B_1C_3$, based on which the experiment was carried out reaching a yield of 88.6%, which was higher than that under all nine experiment conditions. This confirmed that the reaction conditions of $A_2B_1C_3$ to be the optimised conditions for the microwave synthesis of α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid.

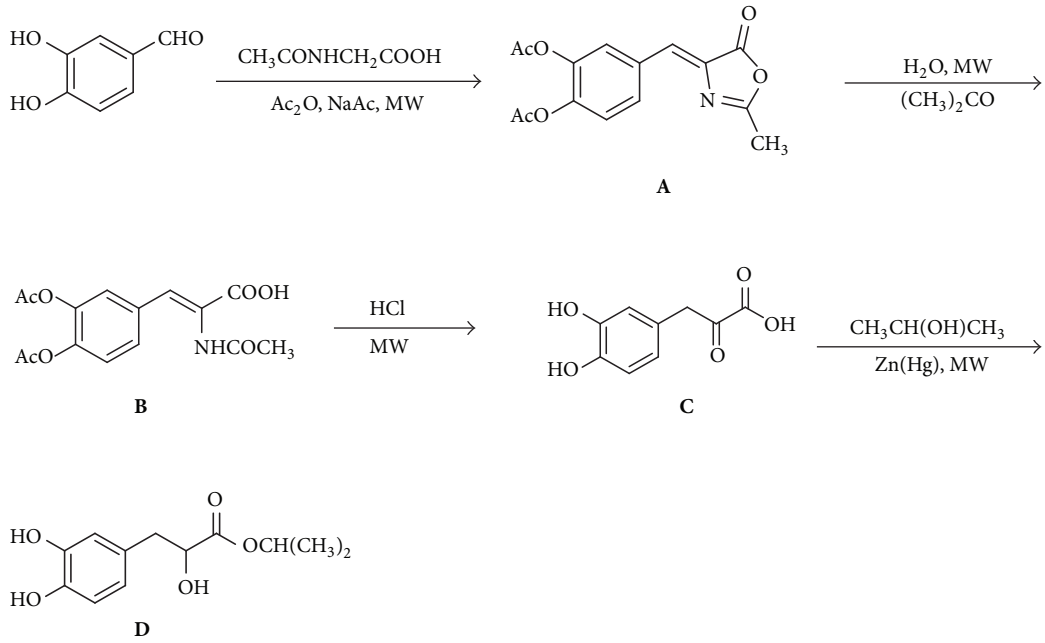
2.4. Synthesis of β-(3,4-Dihydroxyphenyl)pyruvic Acid. It was interesting to note that this step of synthesis required a relatively higher microwave power level. The product was not obtained until a power level of 900 W was applied. Therefore, the power level of 900 W was set throughout the experiment. Table 6 summarises the results at different temperatures for a given reaction time of 30 mins.

Further experiments for different reaction time periods were carried out to explore the highest possible yields. The results are shown in Table 7. It was observed that with increasing reaction time the yield increased. However, when the reaction time exceeded 30 mins, the yield remained approximately constant. This indicated that the highest yield was reached under the reaction conditions of 90°C for 30 mins at a microwave power level of 900 W.

2.5. Synthesis of Isopropyl β-(3,4-Dihydroxyphenyl)-α-hydroxypropanoate. The orthogonal test programs, $L_9(3^3)$, and test results for the synthesis of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate are summarised in Table 8, and the ANOVA results are shown in Table 9.

The variance analysis showed that the three factors had insignificant impact on reaction yields in the chosen level ranges; however, the order of influence was B > C > A; indicating the reaction time to be the dominant factor. The best experiment result (i.e., a yield of 86.1%) from the nine reaction runs was observed under the conditions of $A_2B_3C_1$. However, the design of experiment suggested the optimised experimental conditions of $A_3B_3C_2$. To address the seemly contradictory results in terms of reaction conditions, further three experimental runs were conducted under the ODOE-suggested optimal conditions, and the highest yield of 87.1% was obtained. With that yield (i.e., 87.1%) ODOE was checked which confirmed the optimised microwave reaction conditions of $A_3B_3C_2$ for the synthesis of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate.

It should be noted that the initial design of the reaction time was 10, 20, and 30 mins at microwave power levels of 100, 300, and 500 W, respectively. However, it was found that with 500 W for 30 mins, the reaction product became black due to overheat which was likely attributed to the presence of metallic catalyst zinc amalgam used in this experiment. Therefore, the final reaction time at high power level (i.e., 500 W) was reduced to 25 mins.



Scheme 1: Synthesis route for isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate.

Table 1: Experimental factors and levels.

Reaction	Level	Factor A temperature (°C)	Factor B time (min)	Factor C MW power (W)
Azolactone synthesis	1	128	12	500
	2	138	15	600
	3	148	18	700
Acrylic acid synthesis	1	65	8	300
	2	70	10	400
	3	75	12	500
β-(3,4-Dihydroxyphenyl) pyruvic acid synthesis	1	90	15	900
	2	95	20	900
	3	100	30	900
Isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate synthesis	1	80	10	100
	2	85	20	300
	3	90	25	500

2.6. Comparison of Microwave and Conventional Heating Methods. It is generally understood that the process of microwave radiation heating is different from conventional heating in terms of heat generation and energy transfer [6, 28]. Firstly, microwave heating is a volumetric process and sometimes referred to as "interior heating" where heat can be generated throughout the sample, whilst most of conventional heating relies on conduction and/or convection [29]. This can result in a shorter microwave reaction time due to the quicker heatingup. Secondly, microwave heating is "selective" depending on the materials dielectric properties, suggesting that some microwave strong absorbers can reach higher temperatures than others [29, 30]. This allows to generate possible spatial "hot-spots," for example, on catalyst active sites, leading to an apparent reaction rate acceleration with reference to that at the measured overall temperature. On the other hand, the "selective" heating may also lead to an apparent reaction slowdown where the reaction active sites have lower temperature than the overall temperature.

Table 10 compares the reaction time and yield for the four-step reactions. As can be seen from the Table, it took 5 hrs to carry out the synthesis of azolactone in conventional heating with a yield of 80.0%, while 15 mins with microwave heating gave a yield of 90.8%. Similar results were observed for the synthesis of α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid. More remarkably was the synthesis of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate under microwave heating conditions

Table 2: Orthogonal experiments on synthesis of 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones.

Trial no.	Factor A temperature (°C)	Factor B time (min)	Factor C MW power (W)	Yield (%)
1	1	1	1	80.7
2	1	2	2	86.4
3	1	3	3	82.0
4	2	1	2	84.7
5	2	2	3	89.7
6	2	3	1	82.0
7	3	1	3	85.5
8	3	2	1	82.2
9	3	3	2	87.4
K_1	249.1	250.9	244.9	$K = 760.6$
K_2	256.4	258.3	258.5	$P = 64279.2$
K_3	255.1	251.4	257.2	
U	64289.3	64290.6	64316.7	
Q	10.1	11.4	13.3	

($K = Y1 + Y2 + \cdots Y9$; $P = K^2/9$; ${K_1}^A = Y1 + Y2 + Y3$; ${K_2}^A = Y4 + Y5 + Y6$; ${K_3}^A = Y7 + Y8 + Y9$; ${K_1}^B = Y1 + Y4 + Y7$; ${K_2}^B = Y2 + Y5 + Y8$, ${K_3}^B = Y3 + Y6 + Y9$; ${K_1}^C = Y1 + Y6 + Y8$; ${K_2}^C = Y2 + Y4 + Y9$; ${K_3}^C = Y3 + Y5 + Y7$; $U_A = {K_1}^A + {K_2}^A + {K_3}^A$; $U_B = {K_1}^B + {K_2}^B + {K_3}^B$; $U_C = {K_1}^C + {K_2}^C + {K_3}^C$; $Q_A = U_A - P$; $Q_B = U_B - P$; $Q_C = U_C - P$; $Q_T = W - P$; $Q_E = Q_T - Q_A - Q_B - Q_C$; ${S_A}^2 = Q_A/n_A$; ${S_B}^2 = Q_B/n_B$; ${S_C}^2 = Q_C/n_C$; ${S_E}^2 = Q_E/n_E$; $F_A = {S_A}^2/{S_E}^2$; $F_B = {S_B}^2/{S_E}^2$; $F_C = {S_C}^2/{S_E}^2$).

Table 3: Variance analysis of orthogonal experiments on synthesis of 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones.

Source	Sum of squares	Degree of freedom	Mean square	F value	P value
Factor A temperature (°C)	10.11	2	5.05	0.27	0.788
Factor B time (min)	11.40	2	5.70	0.30	0.767
Factor C MW power (W)	13.27	2	6.63	0.35	0.739
Error	37.55	2	18.77		

to take 25 mins reaching a yield of 87.1% compared to the conventional heating of 10 hrs for a yield of 75.6%. This was likely due to the addition of zinc-mercury amalgam catalyst which is a strong microwave absorber.

For the synthesis of β-(3,4-dihydroxyphenyl) pyruvic acid a shorter reaction was observed with microwave heating. However, the yield under microwave heating conditions was lower than that with conventional heating which may be attributed to the different dielectric properties of the reagents. However, to get a deeper insight into the mechanism of this process further investigation is required.

Table 4: Orthogonal experiment on synthesis of α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid.

Trial no.	Factor A temperature (°C)	Factor B time (min)	Factor C MW power (W)	Yield (%)
1	1	1	1	86.3
2	1	2	2	76.2
3	1	3	3	87.5
4	2	1	2	83.0
5	2	2	3	86.8
6	2	3	1	81.3
7	3	1	3	85.4
8	3	2	1	76.2
9	3	3	2	81.1
K_1	250.0	254.7	243.8	$K = 743.8$
K_2	251.1	239.2	240.3	$P = 61470.9$
K_3	242.7	249.9	259.7	
U	61484.8	61512.9	61542.2	
Q	13.9	42.0	71.3	

Table 5: Variance analysis of orthogonal experiment on synthesis of α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid.

Source	Sum of squares	Degree of freedom	Mean square	F value	P value
Factor A temperature (°C)	13.9	2	6.95	0.63	0.613
Factor B time (min)	41.98	2	20.99	1.90	0.344
Factor C MW power (W)	71.27	2	35.63	3.23	0.236
Error	22.04	2	11.02		

Table 6: Experimental results for synthesis of β-(3,4-dihydroxyphenyl)pyruvic acid at different temperatures.

Level	Temperature (°C)	Yield (%)
1	80	0
2	90	51.3
3	95	33.5
4	100	17.2

3. Experimental

3.1. Materials and Apparatus. 3,4-Dihydroxybenzaldehyde (CP) was purchased from Guangxi Chemicals Import and Export Ltd. *N*-acylglycine (AR) and acetic anhydride (AR) were purchased from Xi'an Chemical Reagent Factory. Mercury chloride (AR) was supplied by Shanghai Shanpu Chemical Reagent Co., Ltd, and Zinc granular (AR) by Xi'an Sanpu

Table 7: Experimental results for synthesis of β-(3,4-dihydroxyphenyl) pyruvic acid at different reaction time periods.

Level	Time (min)	Yield (%)
1	15	9.7
2	20	34.1
3	30	51.3
4	40	51.3

Table 8: Orthogonal experiment on synthesis of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate.

Trial no.	Factor A temperature (°C)	Factor B time (min)	Factor C MW power (W)	Yield (%)
1	1	1	1	48.5
2	1	2	2	83.2
3	1	3	3	57.4
4	2	1	2	49.5
5	2	2	3	59.1
6	2	3	1	86.1
7	3	1	3	69.3
8	3	2	1	57.7
9	3	3	2	80.2
K_1	189.1	167.3	192.3	K = 591
K_2	194.7	200.0	212.9	P = 38809
K_3	207.2	223.7	185.8	
U	38866.2	39343.7	38942.4	
Q	57.2	534.7	133.4	

Table 9: Variance analysis of orthogonal experiment on synthesis of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate.

Source	Sum of squares	Degree of freedom	Mean square	F value	P value
Factor A temperature (°C)	57.2	2	28.6	0.06	0.943
Factor B time (min)	534.7	2	267.3	0.56	0.641
Factor C MW power (W)	133.4	2	66.7	0.14	0.877
Error	955.0	2	477.5		

Chemical Reagent Co., Ltd. Isopropanol (AR) was obtained from Tianjin Chemical Reagent Factory 6.

All microwave-assisted reactions were carried out using a WF-400 Microwave Reaction System (Shanhai Yiyao Analytical Instruments Ltd.) operated at atmospheric pressure. A WRS-1A digital melting point instrument (Shanghai Precision and Scientific Instrument Co., Ltd.) was used for melting point measurements. An RE-52AA rotatory evaporator (Shanghai Rong Biochemical Instrument Factory) and a DZ1-BC vacuum oven (Tianjin Tester Instrument Co., Ltd.) were also used for the experiment. Chemical analysis was performed by both NMR (INOVA-400 MHz, Varian) and infrared spectroscopy (FT-IR360, Nicolet Instrument Co., USA).

3.2. Preparation of 2-Methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones. A mixture of 3,4-dihydroxybenzaldehyde (13.8 g, 0.1 mol), *N*-acylglycine (14.2 g, 0.13 mol), and anhydrous NaOAc (10.7 g, 0.13 mol), Ac_2O (51.2 g, 0.5 mol) was made in a 150 mL double-neck flask. The flask was connected to the microwave reactor system equipped with magnetic stirrers, a reflux condenser and high precision platinum resistance temperature sensors, which was linked with the temperature control system. In a typical process of microwave-irradiated reactions, when the microwave was switched on, the temperature started to rise until it reached the preset level whilst the reaction timing started to count. The temperature control system would switch on and/or cut off microwave irradiation in an intermittent way to keep the temperature in the rage of ±0.1°C at the preset level.

The reaction was carried out in the microwave reactor system under preset conditions. Once the mixture turned into a dark yellow solution with temperature rising, the refluxing started and remained until solution turned dark brown. When cooling to room temperature 60 mL ice water was added, and the mixture was stirred until yellow crystals precipitated. It was then filtered, washed with cold water, and dried under vacuum to produce yellow crystals product A, 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones (mp 161.2–161.5°C, lit. [31] mp 161.0–161.4°C).

3.3. Preparation of α-Acetylamino-β-(3,4-diacetoxyphenyl)acrylic Acid. The above produced 2-methyl-4-(3,4-acetoxybenzylene)oxazol-5-ones (12.54 g, 0.04 mol) was mixed with acetone (46 mL) and water (46 mL) in a 150 mL double-neck flask, which was then attached to the microwave reaction system. With stirring and refluxing, the reaction solution turned dark brown, which was then decolorized using active carbon with microwave heating and refluxing. A vacuumed filtration step followed and resulted in a red solution. When cooling to room temperature needle-shaped yellow crystals formed from the solution, which were then washed with ice water and vacuum filtered resulting in compound B. The filtrate was further concentrated by evaporation, cooled and vacuum filtered to recover yellow product B, α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid (mp 188.8–189.4°C, lit. [31] mp 188.9–189.1°C).

3.4. Preparation of β-(3,4-Dihydroxyphenyl)pyruvic Acid. A mixture of compound B (12.85 g, 0.04 mol) with 125 mL HCl (1 M) was made in a 250 mL double-neck flask, which was connected to the microwave reactor system. When the reaction finished, the light yellow solution was decolorized using active carbon with microwave heating and refluxing, followed by vacuumed filtration. The filtrate was concentrated through evaporation to form light yellow crystals which were further purified by filtration, washing, and drying for product C, β-(3,4-dihydroxyphenyl)pyruvic acid (mp 191.2–191.6°C, lit. [31] mp 191.4–191.6°C).

Table 10: Comparison of reaction results using microwave and conventional heating methods.

Product	Conventional heating		Microwave heating	
	Time (h)	Yield (%)	Time (min)	Yield (%)
Azolactone	5	80	15	90.8
Acrylic acid	4	72.9	8	88.6
β-(3,4-Dihydroxyphenyl) pyruvic acid	8	74.5	30	51.3
Isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate	10	75.6	25	87.1

3.5. Preparation of Isopropyl β-(3,4-Dihydroxyphenyl)-α-hydroxypropanoate. The above synthesised β-(3,4-dihydroxyphenyl)pyruvic acid (1 g) was mixed with 5.5 mL concentrated HCl, 36 mL isopropanol, and 2 g zinc-mercury amalgam in a 100 mL double-neck flask which was connected to the microwave reactor system. Upon the completion of reaction, the reaction mixture was filtrated and distilled to remove catalyst and solvent. After adding 30 mL ethyl acetate, the solution pH was adjusted with saturated sodium bicarbonate to pH < 7 for phase separation. The brown oily phase was then dehydrated with NaS_2O_4 followed by filtration and vacuumed distillation for solvent removal. The product was further purified by hydrothermal recrystallisation to obtain light yellow powder product D, isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate (mp 79.2–80.0°C, lit. [4] mp 79.4–80.2°C).

4. Conclusions

Microwave radiation was employed as an effective heating method in the synthesis of a pharmaceutically active compound isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate. The reaction conditions were optimised by using an orthogonal design of experiment (ODOE) approach, and the operating parameters including reaction temperature, reaction time, and microwave power level were examined. Microwave heating was applied to all four reaction steps and compared to conventional heating method. It was found that the reaction time was significantly reduced for all reactions and the product yields were increased (except the third-step reaction) under microwave heating conditions. The most remarkable microwave enhancement was observed in the step of isopropyl β-(3,4-dihydroxyphenyl)-α-hydroxypropanoate production where the reaction time was reduced from 10 hrs (conventional heating) to 25 mins (microwave heating) whilst the yield was increased from 75.6% to 87.1%, respectively.

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