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Acetaminophen Synthesis Reaction Performance Using Ultrasound, Microwave, and Conventional Methods

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ABSTRACT:

The most widely used antipyretic analgesic drug in the world is acetaminophen. Therefore, this paper shows the synthesis assisted by the conventional, microwave, and ultrasound methods, from p-aminophenol and acetic anhydride, will be analyzed. Three separate mixtures were prepared in flasks, each containing 5,8 g of p-aminophenol, 5 mL of water, and 5,2 mL of acetic anhydride. First, it was subjected to conventional heating at 60 °C for 10 minutes. The second was subjected to microwaves for 5 minutes. The third was subjected to ultrasound for 6 minutes. The yield of the reactions was determined and identified by infrared spectroscopy and assessed by liquid chromatography against a USP primary standard of acetaminophen, giving positive results. The conventional synthesis gave a 56.5% yield and a 90.3% purity of acetaminophen. These results were used as a point of comparison for microwave and ultrasound-assisted methods. The microwave-assisted synthesis yield was 88.9%, and the purity was 98.7%. The yield for the ultrasound-assisted synthesis was 80.3% and the purity was 95.3%. It is concluded that microwave-assisted synthesis shortens the reaction time by 50% and also increases the yield by 32.4% and the purity by 8.4%. Likewise, ultrasound assistance reduced the time by 40%, extending the yield by 23.8% and the purity by 5.0%. Therefore, microwave and ultrasound assistance can be used to enhance the synthesis of acetaminophen and possibly other medicinal compounds that have analgesic and antipyretic effects.

Keywords: Acetaminophen synthesis; Analgesic and Antipyretic; Microwave and ultrasound assisted synthesis; Reaction yield.

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I. INTRODUCTION

The yield of a reaction could be enhanced by utilizing technologies such as microwave and ultrasound. This also is more environmentally friendly and can be conserves resources. In both inorganic and organic chemistry, is a good option to use the microwaves [1–5]. Microwaves are a fraction of the electromagnetic spectrum that covers frequencies between 0,3 and 300 Ghz. Microwave ovens in our homes work at a frequency of 2,45 GHz and the energy associated with this radiation is 0,0016 eV, much less energy than that of a hydrogen bond (0,21 eV). When applying microwaves, resistance is generated in the magnetic field will seek to align polarity, which will generate heat. Currently using microwaves as a synthesis route in the field of Solid-State Chemistry is increasingly investigated. Microwave radiation interacts with matter, giving differences in microwave heating compared to conventional methods, which allows the synthesis of numerous materials in times between 10 and 1000 times less than conventional methods, and the growth of bacteria is also efficiently reduced. particles during the reaction and the size of said particles. Microwave synthesized materials generally do not present significant qualitative disadvantages in terms of crystallinity and physical properties. In some reactions there are even quantitative advances in material properties and attractive particle morphologies. On the other hand, we can consider microwave-assisted synthesis as a fast chemistry method which, also considering the low energy consumption requirements, the technique is compatible with most Green Chemistry principles, since there is no use of toxic or hazardous reagents and solvents, it provides high efficiency because energy consumption is reduced compared to process performance, and the process can be easily monitored to avoid contamination [6–12].

In the pharmaceutical sector, the sonochemistry has achieved a lot of interest [13]. Sonochemistry is the use of

ultrasound to generate chemical reactions and is based on the application of ultrasound to a liquid medium. The ultrasound frequency is in a range of 20 KHz and 10 MHz, associated with a wavelength between 7,5 and 0,015 cm. Considering the wavelength values, there is no direct interaction at the molecular level between the ultrasonic radiation and the chemical species present in the liquid medium of the reaction. Radiation is capable of generating important physical phenomena such as acoustic cavitation capable of altering the chemical nature of the system. During the rupture of a liquid medium, holes or bubbles are produced, this phenomenon is called cavitation and is generated when the pressure reached inside the liquid is sufficiently below its vapor pressure. Cavitation can occur due to a turbulent flow, an electrical discharge, the boiling of the liquid itself or by passing a sound wave through a liquid medium, which causes a series of oscillations of the molecules that make up the liquid, increasing the pressure and temperature. Acoustic cavitation is generated in 3 stages: nucleation, growth and implosion of the bubble, highlighting that the bubbles implode during the compression stages of the acoustic wave, producing high energy that favors the generation of chemical reactions (14). In a large number of heterocyclic compounds with analgesic, antipyretic, anti-inflammatory, antibacterial, and antifungal properties, the application of the ultrasound technique has been a useful form to accelerate and improve their synthesis of them[13].

Acetaminophen was synthesized in 1878 by Morse and used clinically as an analgesic by Von Mering in 1887. Thanks to the studies carried out by Brodie and Axelrod on acetaminophen, it was finally marketed in 1950 in the United States of America, as a non-steroidal, non-opioid analgesic. Acetaminophen is a drug with more than 129 years of clinical use and has been used throughout the world [15–21]. Acetaminophen has properties similar to those of aspirin; however, it does not have peripheral anti-inflammatory properties as well as little effect on platelet function. This medicine has proven to be very effective in the treatment of acute chronic pain. It is also widely recommended in patients with chronic diseases. The American Lung Association recommends it as a first-line medication for pain associated with the flu, and the American Geriatrics Society recommends it for the treatment of mild and persistent pain in the elderly. It is also recommended by the American College of Rheumatology as first-line therapy for osteoarthritis of the hip or knee. Uncontrolled use of this medication can lead to acute liver failure. In 2017, the fever indication was expanded to include patients as young as preterm infants born at 32 weeks' gestation. The maximum total daily dose is 4000 mg and it can be administered in combination with other anti-influenza drugs [22–30]. The synthesis of acetaminophen from p-aminophenol and acetic anhydride is well known and is produced by the acetylation of an amine through a nucleophilic substitution reaction on unsaturated carbon, the nucleophile being the amine. The acetylation mechanism consists of an amine attack on the carbonyl carbon of the acetic anhydride, forming a tetrahedral intermediate, see figure 1 [31]. Although the techniques of ultrasound and microwave have been used in the synthesis of some products, to the date of this investigation there is no evidence of their use in the synthesis of the Acetaminophen.

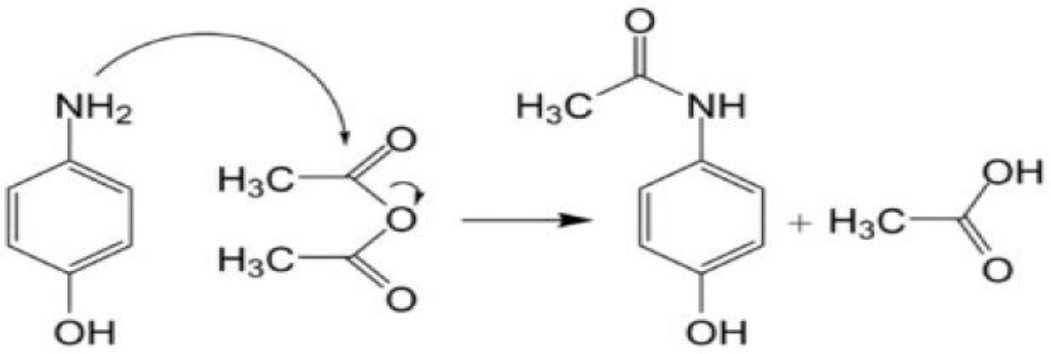

Fig. 1 Synthesis of acetaminophen from p-aminophenol and acetic anhydride

II. MATERIALS AND METHODS

p-Aminophenol, acetic anhydride, water, ice, methanol, USP primary standard of acetaminophen, monobasic potassium phosphate, dibasic sodium phosphate anhydrous Mettler Toledo analytical balance, Shimadzu infrared spectroscope, heating oven, drying oven, microwave equipment, ultrasound equipment and liquid chromatograph.

Conventional synthesis5,8 g of p-aminophenol equivalent to 0,0531 moles were mixed in a heating flask with 5 mL of water and 5,2 mL of acetic anhydride equivalent to 0,0550 moles. The mixture was stirred for 1 minute and heated for 10 minutes at 60°C.

The resulting mixture was cooled by placing it on ice and suction filtered with a Buchner filter. The crystals

retained on the Buchner filter were removed, dried at 105°C to constant weight, and the reaction yield was calculated.

Microwave assisted synthesis

5,8 g of p-aminophenol was mixed in a heating flask with 5 mL of water and 5,2 mL of acetic anhydride. The mixture was stirred for 1 minute and with the help of the microwave it was heated for 5 minutes. The resulting mixture was cooled by placing it on ice and suction filtered with a Buchner filter. The crystals retained on the Buchner filter were removed, dried at 105°C to constant weight, and the reaction yield was calculated.

Ultrasound-Assisted Synthesis

5,8 g of p-aminophenol was mixed in a heating flask with 5 mL of water and 5,2 mL of acetic anhydride. The mixture was stirred for 1 minute and with the aid of ultrasound it was heated for 6 minutes. The resulting mixture was cooled by placing it on ice and suction filtered with a Buchner filter. The crystals retained on the Buchner filter were removed, dried at 105°C to constant weight, and the reaction yield was calculated.

Analytical method

Identification by absorption in the infrared

The absorption was observed in an infrared spectroscope of a mixture prepared with 990 mg of potassium bromide for infrared and 10 mg of acetaminophen primary standard. Similarly, the absorption of a mixture prepared with 990 mg of potassium bromide for infrared and 10 mg of the products obtained with the synthesis methods. [32].

Loss on drying

development of analysis consisted of weighing

approximately 1 g of sample of the product obtained in each synthesis. It dried in a crucible at 105 °C until constant weight. The moisture content is determined by the difference between the weights of the crucible, before and after drying. [32].

Liquid Chromatography Titration

The analysis method used for the evaluation was liquid chromatography, which was established by USP 40 [32]

Solution A: 1,7 g of monobasic potassium phosphate was diluted to 1L with water with 1,8 g of dibasic anhydrous sodium phosphate

Solution B: Methanol

Mobile phase: See table 1

Detector: 230 nm

Column: 4.6 mm x 10 cm; 3.5 µm gasket L7

Flow: 1mL/min

TABLE 1. MOBILE PHASE PROPORTIONS.

Time in minutes	Solution A (%)	Solution B (%)
0	99	1
3	99	1
7	19	81
7.1	99	1
10	99	1

Acetaminophen standard: 10,0 mg of acetaminophen primary standard were weighed and transferred to a 100 mL volumetric flask, 20 mL of methanol were added, stirred for 5 minutes and made up to volume with methanol. It was filtered using a 0,5 µm filter, collecting the filtrate in a 2,0 mL vial. [32].

Acetaminophen sample: 10,0 mg of the product obtained in each synthesis was weighed into individual 100 mL flasks, 20 mL of methanol were added, stirred for 5 minutes and the volume was made up with methanol. The samples were filtered using a 0,5 µm filter, collecting the filtrate in a 2,0 mL vial. [32].

The result % of acetaminophen in the portion taken was calculated with the formula:

Result = (AM/AS) X (CS/CM) x 100%

AM: Sample solution peak area.

AS: Standard solution peak area.

CM: Concentration of sample solution.

CS: Concentration of standard solution.

III. RESULTS AND DISCUSSION

Effect of microwave and ultrasound assistance on the % yield obtained for acetaminophen.

Table 2 shows the yield results obtained for acetaminophen in the different synthesis methods, highlighting the

yield averages obtained in three replicates. Yields of 56,5% are reported for conventional synthesis, 88,9% for microwave-assisted and 80.3% for ultrasound-assisted. The highest yield was obtained in microwave-assisted synthesis, followed by the excellent performance of ultrasound-assisted. However, the good yield of the conventional synthesis is credited because somewhat similar studies found in the literature report a yield of 49,21% [33]. Reaction times were 10 min for conventional synthesis, 5 min for microwave-assisted synthesis, and 6 min for ultrasound-assisted synthesis. These times were fixed since increasing the reaction times does not favor the reaction yield.

TABLE 2. % YIELD OBTAINED FOR ACETAMINOPHEN.

Synthesis methods	Replica	Obtained weight g	Theoretical weight g	% Performance	Average performance	Reaction time in minutes
Conventional	1	6,4116	11,4493	56,0	56,5	10
	2	6,5250	11,4474	57,0		
	3	6,4683	11,4484	56,5		
Microwave	1	10,1907	11,4502	89,0	88,9	5
	2	10,1765	11,4481	88,0		
	3	10,2543	11,4506	89,5		
Ultrasound	1	9,1588	11,4485	80,0	80,3	6
	2	9,2722	11,4471	81.0		
	3	9,1588	11,4485	80.0		

Infrared absorption

Figure 2 shows the infrared spectrum of acetaminophen synthesized by the conventional method and its respective absorption bands, which are the following: 3170.8, 1650.8, 1553.7, 1509.5, 1436.0, 1430.0, 1367.9, 1244,5, 1239,1, 1020,3, 1014,8, 835,8, 835,6, 680,0 and 679,1 cm-1. We also observe in figure 3 the infrared spectrum of the acetaminophen synthesized with the assistance of microwaves with its corresponding absorption bands; 3178,6, 1649,1, 1559,7, 1506,0, 1436,1, 1434,4, 1367,7, 1246,6, 1238,3, 1020,3, 1014,0, 835,1, 683,1 and 680,5 cm-1. Likewise, Figure 4 reveals the infrared spectrum of the acetaminophen synthesized with the help of ultrasound with its reference absorption bands; 3178,6, 1649,1, 1559,7, 1506,0, 1436,1, 1434,4, 1367,7, 1246,6, 1238,3, 1020,3, 1014,0, 835,1, 683,1 and 680,5 cm-1. Table 3 shows a band assigned to nitrogen bonded with hydrogen (NH) at 3172,6 cm-1 and another band assigned to carbon bonded through a double bond with oxygen (C=O) at 1650,3 cm-1.At 1559,6 and 1505,3 cm-1, it observes two bands associated with an aromatic functional group, assigned to the carbon-carbon bond with double bonds (C=C). At 1436,5, 1432,8 and 1368,0, cm-1, three bands associated with the functional group (C-H3) and assigned to the union (CH) are observed. At 1242,5 and 1239,7 cm-1, we observed two bands associated with a hydroxyl functional group assigned to the oxygen-hydrogen (OH) bond. At 1019,4, 1015,9 and 801,3 cm-1, we observe three bands assigned to carbon-nitrogen bonding by a single bond (CN). At 681,5 and 680,7 cm-1, we observe two bands assigned to the carbon-nitrogen-carbon bond by a single bond (CNC). The absorption bands of the samples were compared against the absorption bands of the primary standard of acetaminophen, thus corroborating that the product obtained in the synthesis methods is acetaminophen. Figure 5 shows the infrared spectrum and the absorption bands of the functional groups belonging to the primary standard acetaminophen molecule, highlighting that this is a secondary amide which presents assigned bands typical of the molecule.

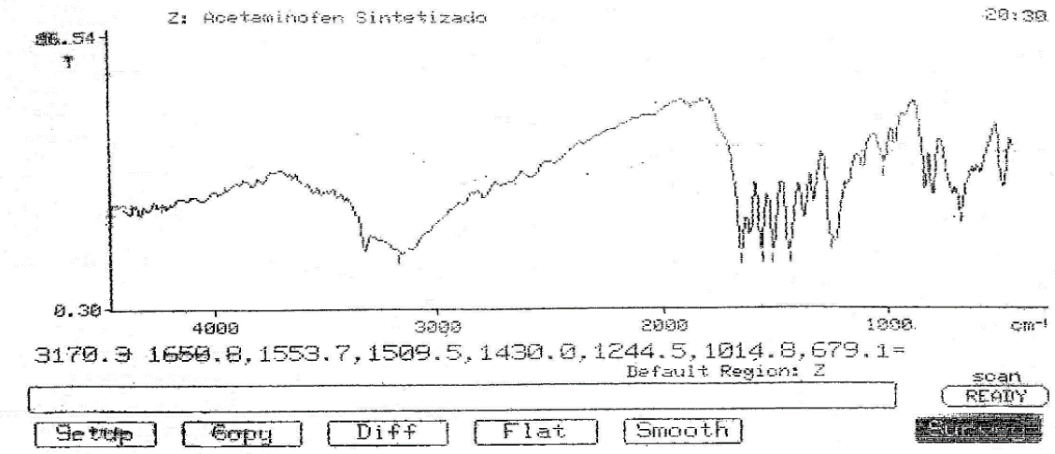

Fig. 2Infrared spectrum of acetaminophen synthesized by conventional method

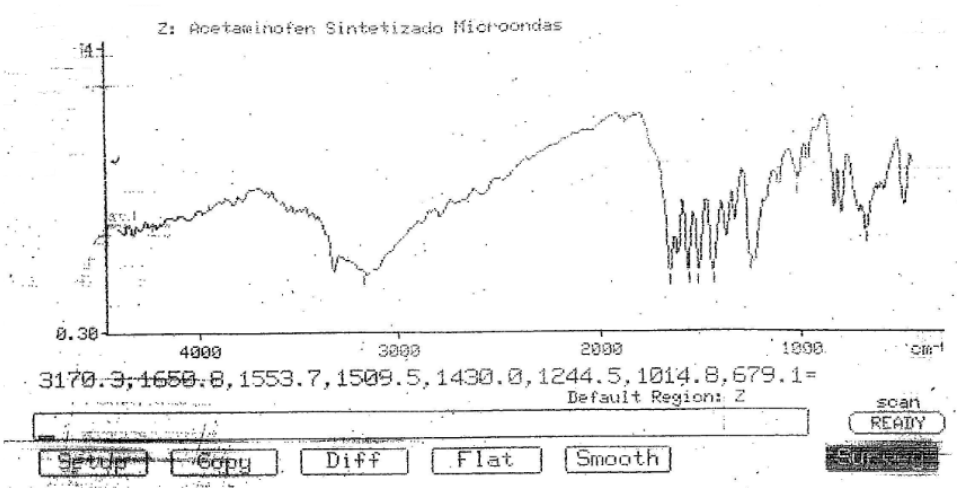

Fig. 3Infrared spectrum of acetaminophen synthesized by microwave-assisted method

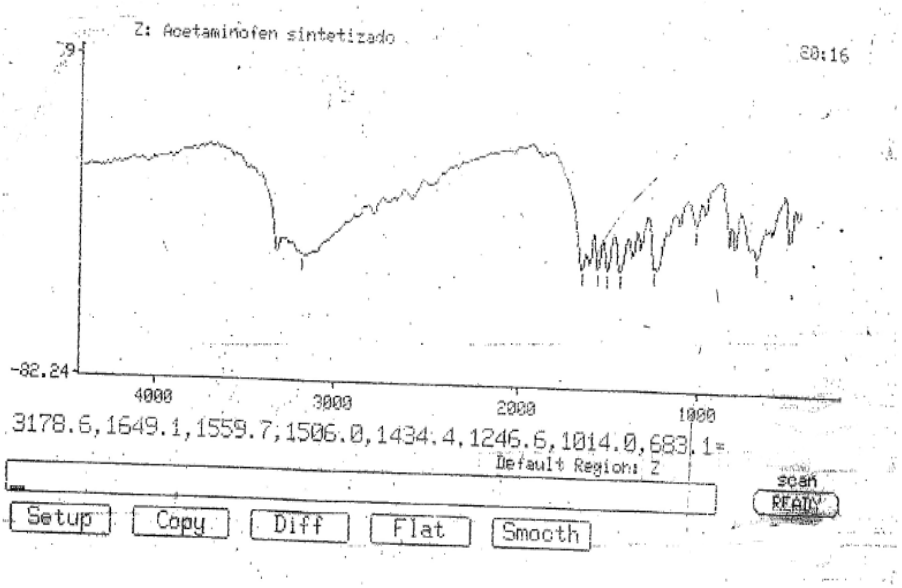

Fig. 4Infrared spectrum of acetaminophen synthesized by ultrasound-assisted method

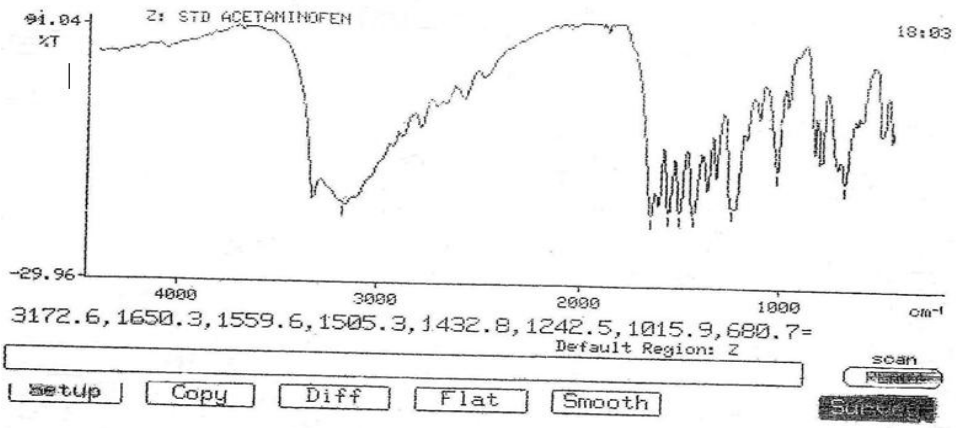

Fig. 5Infrared spectrum of acetaminophen primary standard

TABLE 3. INFRARED FUNCTIONAL GROUPS.

Family	Functional group	Band (cm-1)	Assignment
Amides	RCONHR´ (Secondary)	3172,6	vNH
Ketones	C=O	1650,3	vC=O
Aromatic		1559,6 and 1505,3	vC=C
Alkanes	C-H3	1436,5, 1432,8 and 1368,0	$^{\delta}$ CH asim
Alcohols and Phenols	ROH and Phenols	1242,5 and 1239,7	v OH
Nitro compounds	aromatic	1019,4, 1015,9 and 801,3	vCN
Nitro compounds	aromatic	681,5 and 680,7	cnc
v = stress mode asym = asymmetric $^{\delta}$ = strain mode			

Loss by oven drying

In order to guarantee the quality of the acetaminophen, it should not have a humidity greater than 0,5% [32]. Table 4 shows the averages of the results of three replicates of the loss on drying of acetaminophen according to its synthesis method. These results were satisfactory because none was greater than 0,5%.

TABLE 4. LOSS ON DRYING ACETAMINOPHEN

Synthesis methods	Replica	% Loss on drying	Average % loss on drying
Conventional	1	0,3	0,3
	2	0,2	
	3	0,3	
Microwave	1	0,2	0,2
	2	0,2	
	3	0,3	
Ultrasound	1	0,2	0,3
	2	0,3	
	3	0,3	

4.4. Purity or titration of acetaminophen by liquid chromatography

With the intention of certifying the quality of acetaminophen, its purity must not be less than 98,0% nor greater than 102.0% calculated on a dry basis [32]. Table 5 shows the average of three replicates of the % purity of the acetaminophen obtained in the different synthesis methods. The purity averages obtained in the different synthesis methods stand out, reporting 90,3% in conventional synthesis, 98,7% for microwave-assisted and 95,3% for ultrasound-assisted. The highest purity was obtained in the microwave-assisted synthesis, followed by the ultrasound-assisted synthesis and ending with the conventional synthesis, which presented the lowest purity. %RSD results below 2,0% for all three replicates in each synthesis method ensured method reproducibility.

TABLE 5. % PURITY OF ACETAMINOPHEN.

Synthesis methods	Replica	% Purity acetaminophen	Average %	%RSD
Conventional	1	90,3	90,3	0,3
	2	90,5		
	3	90,0		
Microwave	1	98,8	98,7	0,2
	2	98,7		
	3	98,5		
Ultrasound	1	95,2	95,3	0,2
	2	95,5		
	3	95,2		

IV. CONCLUSION

It concludes that the Microwave and ultrasound techniques were used successfully overcoming the conventional method because they enhanced the yield and purity of acetaminophen synthesis using p-aminophenol and acetic anhydride. In this research, is evidence that reaction times in the synthesis of acetaminophen would be reduced by the use of these techniques, which contribute to an improvement in the performance of the reaction. The results of 56,5% yield and 90,3% purity of acetaminophen, obtained in 10 minutes by conventional synthesis, were used as a point of comparison for the microwave and ultrasound methods. The improvement obtained in the parameters reveals that the % yield of the reaction was 88,9% and the purity of 98,7% was possible in 5 minutes of microwave reaction, shortening the time by 50%, increasing the yield by 32, 4%, and the purity at 8,4%. Likewise, there was improve in the yield percentage of 80,3% and a purity of 95,3% in 6 minutes of reaction in ultrasound, reducing the time by 40%, extending the yield by 23,8%, and the purity to 5,0%.

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