A Relatively Mild Preparation Method for Aspirin Copper Using Resin Catalyst

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Abstract: Aspirin copper is a new derivative of aspirin. Compared to aspirin it shows strong clinical anti-inflammatory and analgesic functions, but also shows less toxic side effects, so it has been widely concerned by scholars in medical and chemical fields all over the world. In this paper, salicylic acid and acetic anhydride were used as raw materials, and strong acidic cation exchange resin was used to replace the traditional catalyst to prepare aspirin with high yield and high purity under mild conditions at 70℃ . Then, the target product, copper aspirin, was obtained by accurately adjusting the pH of the solution and further reacting with copper sulfate. By adjusting the ratio of raw materials, reaction temperature, solution pH, reaction time and other factors, the results showed that the optimal reaction conditions were as follows: under the environment of 15 ℃ and pH 7, the copper aspirin obtained by fully reacting with aspirin and copper sulfate at the ratio of 2:1 for 40 min had excellent purity and yield. Besides, the final product was analyzed qualitatively and quantitatively by iodimetry, and the intermediate product and the target product were analyzed accurately by infrared and high performance liquid chromatography. The results showed that the titration method was consistent with the data obtained by high performance liquid chromatography, the purity of aspirin copper was 85%, and the yield was up to 98%. The above method has the advantages of high yield, good product quality, low pollution, low energy consumption and high safety, and has a good industrial prospect.

Keywords: Salicylic acid; Aspirin; Aspirin copper; Resin

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1. Introduction

Aspirin (acetylsalicylic acid) is a white crystalline powder that has been used in the medical field for a hundred years. It is one of the three classic drugs in the history of medicine. Currently, aspirin is the earliest and most widely used antipyretic and analgesic drug in clinical practice. [1] It not only has the effects of antipyretic and analgesic, cancer treatment, and immune therapy, but also has the effects of prolonging the flowering time of flowers and removing fabric stains.[2,3]

Aspirin copper is a derivative of aspirin. In animal models, aspirin copper has significantly higher anti-inflammatory and antiplatelet aggregation activities than aspirin, with minimal gastrointestinal side effects and antiulcer formation. [4] It is a highly promising drug for development and application.

Recently, country over the world has a solid research foundation for the synthesis of aspirin and aspirin copper technology, especially for the synthesis of aspirin technology has been relatively mature.[5] Most of the salicylic acid and acetic anhydride as raw materials, acid as a catalyst, under heating conditions to synthesize aspirin. However, the traditional method has many by-products and low yield, which restricts the development of aspirin and its derivatives. Therefore, many researchers began to focus on the study of different catalysts, and some theoretical results have been achieved in aspirin catalytic synthesis. In the process of synthesizing copper aspirin, the alkaline environment is mainly used to increase the solubility of aspirin in solution, and further generate sodium aspirin salt, and then the coordination

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and complexation reaction with a certain proportion of soluble copper salt (such as copper sulfate, etc.), and finally the bright blue crystalline powder of copper aspirin is prepared.[6,7] Nevertheless, the synthesis of aspirin copper is still under exploration and research. The key point of the coordination process is how to form an accurate and stable complex. Herein, it is of great significance to seek a green, stable and convenient experimental synthesis scheme. [8]

In this paper, the traditional process using concentrated sulfuric acid as catalyst is abandoned, and acidic cation exchange resin is used instead. The shortcomings of concentrated sulfuric acid as a strong corrosive agent are improved, and the performance of acidic cationic resin can be compared with concentrated sulfuric acid beautiful, and has the advantages of conducive to recovery, better control the amount of catalyst, and can be reused for several process cycles. At the same time, it also effectively solved the problem of waste disposal. For the reaction, the catalyst has higher selectivity for the required products and less by-products, which is a clean, green and safe production process with high reaction efficiency and high yield expected by the experiment.

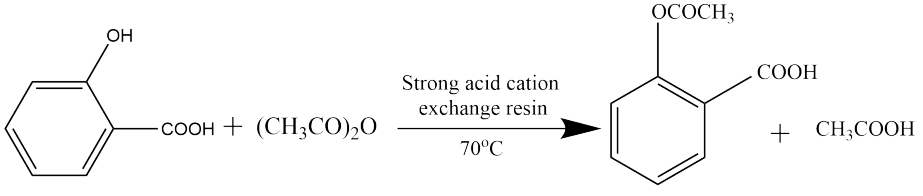
2. Experimental Section

(1) Materials

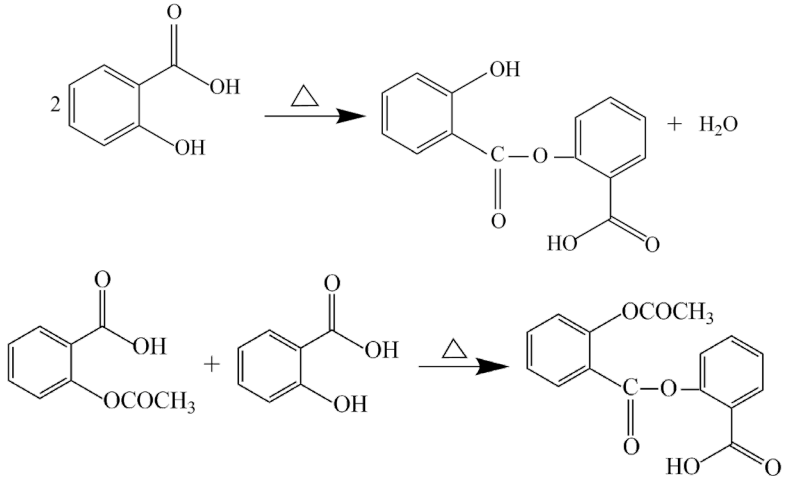
All involved reagents and chemicals were of commercial grade and used directly without further purification.

(2) Methods

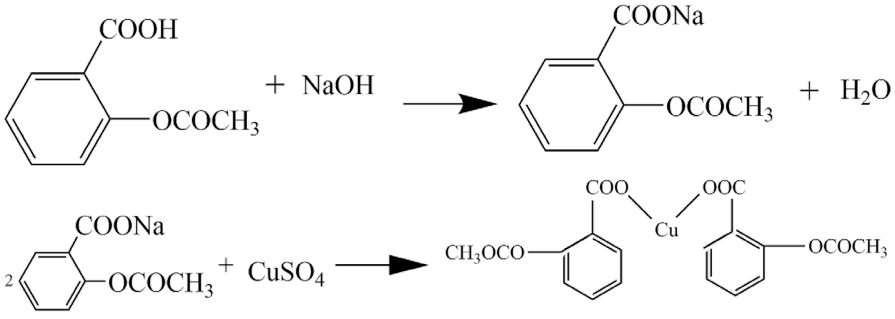
The whole process of synthesizing the product was mainly divided into two steps. First, acylation of salicylic acid with acetic anhydride catalyzed by an acidic cation exchange resin. The reaction equation is shown below.



Then salicylic acid reacts with acetic anhydride, through acetylation reaction, the hydrogen atom on the phenol hydroxyl group of salicylic acid molecule was replaced by acetyl group, and acetylsalicylic acid was generated. In order to accelerate the reaction, a small amount of strong acidic cation exchange resin was added as catalyst. The catalyst will destroy the hydrogen bond formed between hydroxyl group and hydroxyl group in salicylic acid molecule, so that the acylation reaction was easier to complete.[9] However, at the same time of generating acetylsalicylic acid, condensation reaction can also occur between salicylic acid molecules to form a small amount of polymer. Possible side effects are shown below:



On the basis, copper aspirin was obtained by the bridge bidentate coordination with copper sulfate, as shown below.



The specific steps and processes of the experiment are as follows:

Synthesis of Aspirin: Briefly, 10 g salicylic acid and 13.6 mL acetic anhydride solution (n/n=1/2) were mixed into a round bottom flask then added 0.5 g acid cation exchange resin as catalyst. The solution was reaction at 70℃ for 20 min under stirring. The cation exchange resin is filtered out while hot, and the catalyst and reaction solution were separated. 75.0 mL distilled water was added to the reaction solution and cooled in the ice water bath for 20 min, waiting for the crystal to precipitate. After extraction and filtration, the crude aspirin product was obtained.

Refining of Aspirin: The crude aspirin product was transferred into beaker and 10 mL ethanol was added. It was placed in a water bath temperature of 35℃ to accelerate the dissolution, after complete dissolution, room temperature cooling, until the crystal precipitation, after pumping and filtering, to obtain bright white crystals.Next, transferred to the conical flask, 100 mL saturated sodium bicarbonate solution was added with a glass rod constantly stir until no air bubbles. After suction filtration, a clarified filtrate was received. Then concentrated hydrochloric acid was dropped in order to adjust pH to below 2. When white crystals formed, filtered and washed several times with the DI water to wash away the interference of chloride ions. Natural air drying results in bright white refined crystals.

Synthesis of Aspirin Copper: Added the sodium hydroxide solution (1.26 mol/L) to the supersaturated ethanol solution of aspirin, stirred while adding until the aspirin is completely dissolved. During this process, the reaction temperature was controlled below 20 ℃ , and the pH of the reaction solution was about 7, to prevent aspirin from hydrolyzing and formed sodium aspirin solution. Then drop 27 mL CuSO4·5H2O (1.25 mol/L) solution into sodium aspirin solution with the constant stir, produced a bright blue precipitate. Filtered and rinsed with DI water to obtain crude aspirin copper, cleaned with DI water and ethanol three times in turn, filtered to get bright blue crystalline aspirin copper.

(3) Apparatus and measurements

The resulting aspirin and aspirin copper were studied using Fourier transform infrared spectrometers analysis, scanned across the 400-4000 cm^{-1} wavenumber range. The content of copper in aspirin was determined by the combination of instrument analysis and chemical analysis, and the qualitative and quantitative results of iodimetry were further verified by HPLC.

(4) Determination of aspirin copper

The Iodometric titration for purity: Titration is a chemical assay used to determine the purity of aspirin copper. First, 0.5 g soluble starch and 5 mL DI water were mixed up and gently poured into 100.0 mL boiling water, stir along, boil for 2 min, then cool it down set aside for next, it was named new starch indicator. Second, the prepared aspirin copper (1.0 g), 5 mL H_2SO_4 (3 mol/L) and 30 mL DI water were heat and boil for 3 min, after full reaction, add 15 mL DI water shake well and cool to room temperature. Finally add 1.5g potassium iodide, shake it well and set aside.

Titrate with 0.1 mol/L sodium thiosulfate standard solution until the solution turns light yellow, add 10 mL

KSCN reagent (100.0 g/L), and add 2.0 ml 0.5% starch solution, continue to titrate with sodium thiosulfate standard solution until the blue color just disappears and the end point (blue color does not return within 30s). The volume of sodium thiosulfate solution consumed was recorded and titrated three times in parallel to calculate the copper content in the product.

The calculation of the purity in product by the following equation:

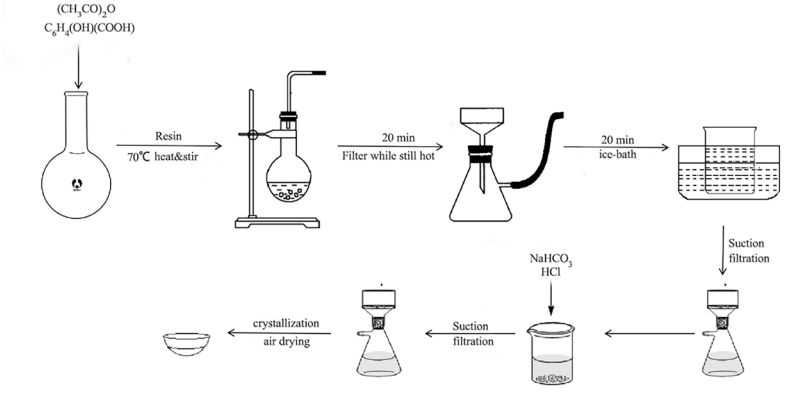
$$Cu\% = \frac{c(Na_2S_2O_3) \times V(Na_2S_2O_3) \times M(Cu)}{m_s \times 1000} \times 100\%$$

Where c, V, M and m_s represent concentration, volume, relative atomic mass and the mass of aspirin copper, respectively.

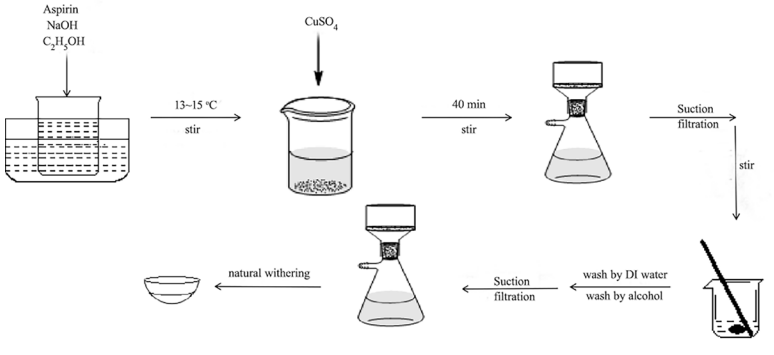
The Calculation for yield: Theoretically speaking, according to the reaction equation, take 10 g salicylic acid as an example, it should get 30.5 g aspirin copper under no special circumstances, the calculation for yield by the following equation:

$$y\% = \frac{Actual\ output}{theoretical\ output} \times 100\%$$

3. Result and Discussion



Scheme 1. Schematic illustration of the synthetic processes of Aspirin



Scheme 2. Schematic illustration of the synthetic processes of Aspirin Copper

Scheme 1 and Scheme 2 show the whole process of preparing aspirin copper product with salicylic acid as raw material. See *2.2 Methods* for specific experimental procedures.

(1) Single factor analysis

The effects of feed ratio, temperature and reaction time on the synthesis purity and yield of aspirin and aspirin copper were studied in a single factor experiment.

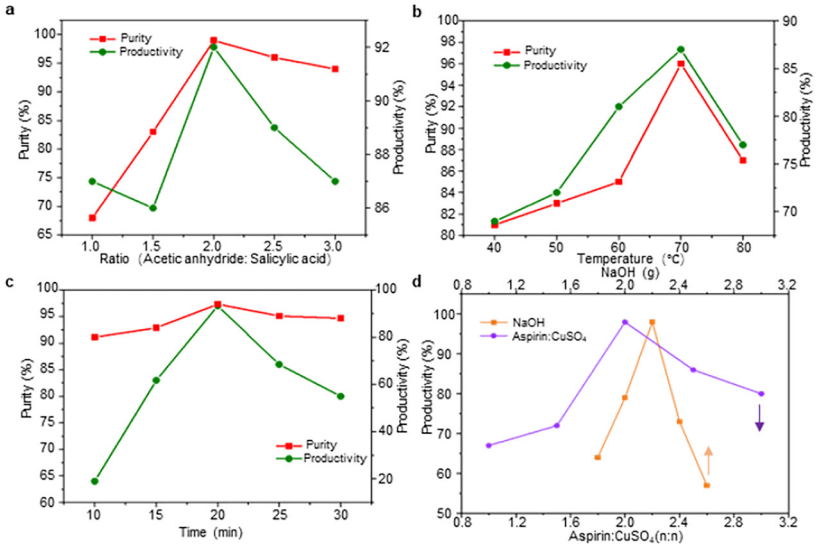


Figure 1. (a) Effect of raw material ratio on purity and productivity of aspirin. (b) Effect of reaction temperature on the purity and productivity of aspirin. (c) Effect of reaction time on aspirin purity and productivity. (d) Effect of sodium hydroxide dosage and raw material ratio on productivity of aspirin copper.

As shown in Figure 1a, with the increase of the proportion of raw materials, the purity and productivity of aspirin showed a trend of increasing first and then decreasing, while other variables were controlled uniformly. When the ratio of raw material reached 2 ($n_{\text{acetic anhydride}}$: $n_{\text{salicylic acid}}$ = 2:1), the purity and productivity reached the highest values of 99% and 92%, respectively. So with 10 g (72 mmol) of salicylic acid as the basis, in order to maximize the purity and productivity the required acetic anhydride dosage is 13.6 mL (144 mmol), that is, the optimal raw material ratio is 2:1.

The effects of different reaction temperatures on the purity and productivity of aspirin are shown in the Figure1b. During the reaction process, with the increase of reaction temperature, the product purity and productivity of aspirin increased first and then decreased. When the reaction temperature reached 70℃, the productivity of aspirin reached the maximum of 91% and the purity was as high as 99.98%. This is mainly because at low temperatures, the reaction rate is slower and therefore the reaction material does not react completely at the same time. When the temperature is too high, it will lead to excessive by-products, thus reducing the purity and productivity of the reaction. In addition, we also explored the effect of reaction time, as shown in Figure1c. It can be seen that the optimal reaction time for salicylic acid to react with acetic anhydride is 20 min, and the purity of aspirin can reach 97%, but the change of time has little effect on the yield. This may be because the reaction time is too short, the raw material reaction is not complete, when the reaction time is more than 20 minutes, the rate of side reaction will be accelerated, and the acylation reaction is a reversible reaction, but the reaction time is too long will lead to the decline of aspirin purity. Therefore, when the reaction time is 20 minutes, the acylation reaction can be more complete, and the degree of hydrolysis of salicylic acid under high temperature can be controlled less, and the side reaction is relatively reduced.

After the optimum preparation conditions were obtained, aspirin with high purity was synthesized. On this basis, aspirin reacted with copper ion to prepare copper aspirin under alkaline conditions. In this process, we also investigated the effect of reaction temperature on copper aspirin during this process that shown in Table S1. The results showed that when aspirin and sodium hydroxide were completely dissolved at 15℃, the yield and purity of copper aspirin were the best. The temperature is too low to dissolve all and therefore the reaction is not effective,

while the temperature is too high, aspirin copper will hydrolysis to produce aspirin, so the conversion is not good, the yield is low, and the impurity content is high. Similarly, the amount of sodium hydroxide also needs to be reasonably regulated.

The concentration and dosage of sodium hydroxide also have obvious influence on the yield as shown in Figure 1d and Table S3. When the amount of sodium hydroxide is low, the filtrate appears baby blue, while the amount of sodium hydroxide is excessive, the filtrate shows obvious green, and the higher the concentration of sodium hydroxide, the darker the color. This is mainly because when the sodium hydroxide is added, the carboxylic acid in aspirin is converted to carboxylic acid less content, so it is not completely with copper ion coordination, so that there is still a small amount of copper ion in the filtrate and appear blue. When the amount of sodium hydroxide is too much and the solution is too alkaline, the ester group of aspirin is hydrolyzed, and the resulting salicylic acid is coordinated with copper ions to form a green complex, resulting in a green. When the dosage of sodium hydroxide is appropriate, it can not only make aspirin to acetyl salicylate sodium and copper ions just completely reaction and almost no aspirin ester group is hydrolyzed, so the filtrate is colorless, at this time aspirin copper purity and high yield are highest. Next the influence of feed ratio was further studied. The theoretical molar ratio of the reaction between sodium aspirin and Cu^{2+} is 2:1, according to which copper aspirin was synthesized in the literature.[10,11] According to this molar ratio, the yield in this experiment is similar to that in the literature.[12] It can be seen that the content of copper sulfate has little effect on the content of copper aspirin, and the content of aspirin has a great effect on the content of copper aspirin. Aspirin overdose by 50% will greatly reduce the purity of copper aspirin, and the yield of copper aspirin obtained at the molar ratio of 2:1 is the best.[13]

(2) High pressure liquid chromatography (HPLC)

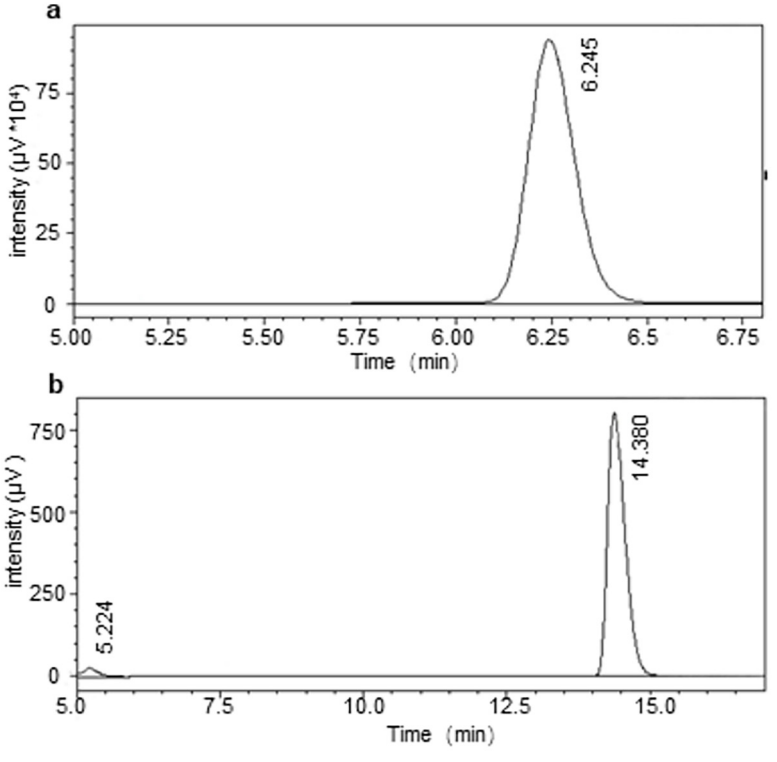


Figure 2. (a) HPLC of aspirin. (b) HPLC of aspirin copper.

The sample solution of 10 μL was injected into the high performance liquid chromatography, the chromatogram was recorded, and the content was determined by external standard method. The chromatographic column selected for testing aspirin was as follows: Agilent 1200-C18 (4.6mm * 250mm, 5μm), the mobile phase was

methanol/water/glacial acetic acid =70/30/0.6, the test was conducted at the flow rate of 0.5mL /min, the detection wavelength was set at 280 nm, and the column temperature was set at 30℃ . The chromatographic column selected for the test of aspirin copper was octadecylsilane bonded silica gel column, the mobile phase was methanol/water/tetrahydrofuran/glacial acetic acid =45/52.5/2.5/0.5, and the detection wavelength was 276nm. The test results were shown in Figure 2 that the resultant aspirin content is 99.391% according to the conversion formula.[14,15] The content of copper ion in aspirin copper products was also determined by HPLC. It was observed that copper aspirin peaked at 14.380 s, and the copper content in the sample was obtained according to the copper ion area and converted to copper aspirin content that was 85.988 %. The copper ion content of the product did not reach the theoretical value, it is speculated that the neutralization reaction was not sufficient, and the precipitation speed was too fast during the precipitation process, which wrapped the aspirin solution, resulting in the residual aspirin.[16] In addition, during the reaction process, aspirin was soluble in ethanol and copper sulfate was soluble in water, and the molar ratio of the ingredients in the synthesis was 2:1. Even if there is a small amount of residual between the two can be washed off during washing, the impurity salicylic acid has a maximum absorption at 230 nm UV, and the minimum detection limit is 0.04 mg/L, so at 3.147 s, there is a peak of salicylic acid, which reduces the purity of the product.[10]

(3) Fourier transform infrared spectrophotometer (FTIR)

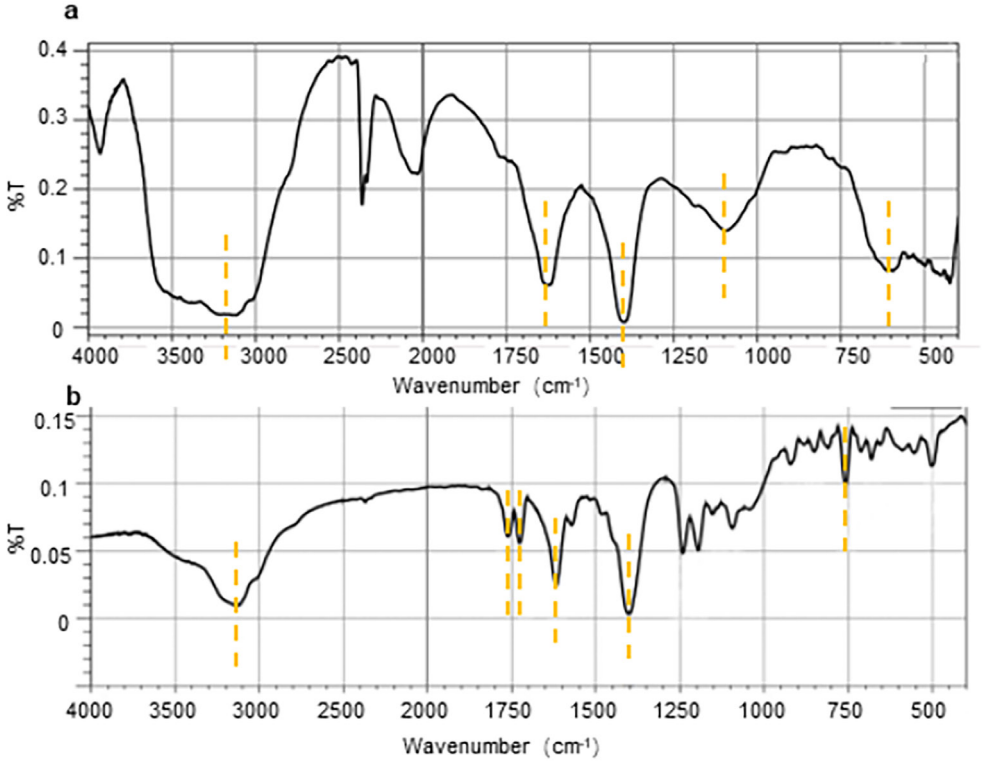


Figure 3. (a) FTIR spectra of aspirin. (b) FTIR spectra of aspirin copper.

In order to further demonstrate the chemical structure of the product, we performed infrared analysis of the product under the same conditions as standard aspirin. The results are shown in Figure 3a. Under the infrared spectrum, the infrared curve of our product is basically consistent with the standard curve of aspirin. The wide peaks at 3400 cm^{-1} - 3200 cm^{-1} belong to the absorption peak of -OH association in carboxyl group. The single peak at 1900 cm^{-1} - 1600 cm^{-1} belongs to the C=O stretching oscillation, which proves the existence of the C=O group. There are multiple absorption peaks in 1600 cm^{-1} - 1500 cm^{-1}, which is the universal spectrum of benzene ring, proving the existence of benzene ring. At 1000 cm^{-1} - 1250 cm^{-1} is the characteristic peak of C-O. The presence of R-CH3 can be determined by the presence of multiple absorption peaks between 700 cm^{-1} and 850 cm^{-1}. To sum up, it can be determined that in this experiment, the product obtained under the catalytic condition of acidic cationic resin is

high-purity aspirin, and its structure is highly similar to that of commercially available aspirin standard samples.[17]

Similarly, the refined aspirin product and the standard sample of aspirin copper were analyzed by infrared spectroscopy, and the results were shown in Figure 3b. 1726.4 cm^{-1} belongs to the absorption peak of -C-O-C group; In the range of 1617.25-1760.88 cm^{-1}, there are multiple absorption peaks, which is the characteristic peak of the benzene ring. 1242.38 cm^{-1} has a strong absorption peak of -CO group in the range of 1000-1300 cm^{-1}; 758.35 cm^{-1} is the ortho-substituted absorption peak of benzene ring. The strong absorption peak of 3123.9 cm^{-1} belongs to the -CH group on the benzene ring. In summary, the analytical results can be confirmed by comparing the standard infrared absorption spectra of aspirin copper.

4. Conclusion

In the synthesis route of aspirin, 10 g salicylic acid was used as the base material, the optimal ratio of salicylic acid to acetic anhydride was 1:2, that is, 15.0mL, the optimal reaction temperature was 70℃ , and the optimal reaction time was 20 minutes under stirring conditions. The yield of the obtained aspirin product can reach 92%, and its purity can be as high as 99.98%. Furthermore, copper aspirin was synthesized from aspirin at an optimal water bath temperature of 15℃ . In this process, 2.22 g sodium hydroxide and 10 g aspirin were reacted in a ratio of 2:1 with 27 mL Copper sulfate. The best reaction conditions resulted in a yield of up to 98% and purity of 85% for copper aspirin.

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