Improvement of Synthetic Method of Lysine Aspirin

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Abstract. The synthesis method of lysine aspirin was improved, and the new method was applied to the synthesis of similar new drugs. Aspirin is reacted with an aqueous solution of sodium hydrogen carbonate to prepare its sodium salt, and lysine was reacted with a sodium salt thereof in water to prepare lysine aspirin. The product was identified by melting point, infrared spectroscopy and high performance liquid chromatography; the cysteine salts of aspirin was prepared by this method, and the product was identified by micro melting point apparatus and infrared spectroscopy. Lysine aspirin was synthesized by the reaction of sodium acetylsalicylate with lysine. The author measured the melting point and infrared absorption spectrum of the cysteine salt sample of aspirin, which was initially determined to be possible. The new method offers the possibility to expand the production route of lysine aspirin, and also provides new ideas for the preparation of similar new drugs.

1. Introduction
Aspirin is an earlier, broader and more common antipyretic analgesic and anti-inflammatory drug. The drug has a wide range of pharmacological effects, including alleviating skin and Kawasaki disease, inhibiting platelet aggregation, and preventing digestive tract tumors. It also has the advantages of rapid efficacy, stable efficacy, and few allergic reactions. This not only brings a wide range of clinical applications, but also brings adverse reactions that cannot be ignored. Adverse reactions such as gastric ulcer, gastric hemorrhage, aspirin triad, salicylic acid reaction, etc., have greatly limited the clinical application of aspirin [1, 2]. In addition, aspirin is poorly water-soluble and cannot be formulated into injections, granules, and the like which require a certain water-soluble form of the drug, which limits the route of administration.

Amino acid is the basic unit of protein molecules in living organisms. It has special physiological functions in living organisms and is one of the indispensable nutrients in living organisms. Among the natural amino acids, 20 kinds of amino acids are involved in protein synthesis. Amino acids can also act as glucose substrates, carriers of nitrogen, neurotransmitters, and are related to protein turnover, enzymatic activity, and ion flux regulation. Humans have a wide range of amino acid requirements and their applications in the field of medicine are increasing day by day. Amino acid derivatives play an indispensable role in the treatment of hepatic diseases, cardiovascular diseases, ulcerative diseases, nervous system diseases and inflammation [3]. In addition, amino acid derivatives can also be used as antibacterial synergists. Nowadays, amino acid derivatives have been widely used as antitumor drugs [4]. This indicates that the application prospect of amino acid derivatives is very broad.

Lysine aspirin is a complex salt of aspirin and lysine. It is an ideal water-soluble aspirin salt. The drug not only has antipyretic and analgesic effects, but also is a good drug for the treatment of
cardiovascular diseases. Its antithrombotic effect and reduction of atherosclerosis are better than aspirin [5]. This drug is mainly used for intramuscular or intravenous injection to avoid gastrointestinal disorders caused by oral aspirin. Therefore, lysine not only reduces the adverse reactions of aspirin, but also increases the solubility of aspirin in water and the route of administration. However, the method described in the literature [6, 7, 8] shows that the existing synthetic route of lysine aspirin need to use various organic solvents, which will inevitably lead to many problems such as solvent residue. Therefore, this project is based on the existing lysine aspirin synthesis method [6, 7, and 8] and other similar drug synthesis methods [9] to find a more suitable synthesis method, in order to further improve the synthesis method of lysine aspirin and try to apply this method to the synthesis process of similar drugs.

2. Materials and methods

Lysine aspirin for injection was obtained from Shanxi Pude Pharmaceutical Co., Ltd. (product batch number: 04130602). Sodium bicarbonate (NaHCO3), acetylsalicylic acid (aspirin) were provided by Pine Chemical company (China). Lysine, cysteine and other chemicals were provided by Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All reagents are of analytical grade.

3. Preparation of sodium acetylsalicylate (aspirin sodium salt)

Weigh accurately 0.2531 g (3 mmol) of sodium hydrogen carbonate, add 4 ml of distilled water, stir to dissolve, and then accurately weigh 0.6255 g (3.5 mmol) of acetylsalicylic acid, add it to an aqueous solution of NaHCO3, and stir to fully react. When the bubble is no longer generated, stop stirring, let stand, and filter. The filtrate was transferred to the evaporating dish and evaporate at 50 ℃ to remove water. After evaporation to dryness and cooling to room temperature, a solid substance (sodium acetylsalicylate) was scraped from the evaporating dish. The yield was 68.46%.

![Fig. 1 Scheme of sodium acetylsalicylate](image1)

4. Synthesis of lysine aspirin in non-organic solvent

0.3007 g (1.5 mmol) of sodium acetylsalicylate was accurately weighed, and 1 ml of distilled water was added thereto, and the mixture was sufficiently dissolved by stirring, allowed to stand, filtered, compounded with a concentration of about 30% sodium acetylsalicylate solution, stand by.

Method 1: The aqueous solution of sodium acetylsalicylate and lysine was added to a round bottom flask, heated in a water bath at 60 ℃, and refluxed for 40 min. Remove the reflux device, wait until the reaction solution is cooled to room temperature, transfer to a 10 ml glass vial, put it at room temperature for 24 h, then evaporate the water at 50 ℃ until solid substances precipitate, stop heating, cool to room temperature, place it in the refrigerator at 0-5 for 24 hours to make it fully crystallize, and the filter cake was dried by suction to obtain a white powdery reaction product, namely lysine aspirin (containing a small amount of lysine). The yield was 88.48%.
Method 2: Mix the aqueous solutions of the above two reactants, stir them to make them evenly mixed, transfer them to a 10 ml glass vial, leave them at room temperature for 48 hours, then remove the water by evaporation in a 50 °C water bath until the solid matter is precipitated, stop heating, cool the mixture was allowed to stand at room temperature for 24 hours in a 0-5 °C freezer to be crystallized, suction filtered, and the filter cake was dried to get the white powdery reaction product, lysine aspirin(Containing a small amount of lysine). The yield was 53.46%.

5. Synthesis of cysteine salt of aspirin in non-organic solvent

0.3007 g (1.5 mmol) of sodium acetylsalicylate was accurately weighed, and 1 ml of distilled water was added thereto, and the mixture was sufficiently dissolved by stirring, allowed to stand, filtered, compounded with a concentration of about 30% sodium acetylsalicylate solution, stand by. The specific steps of Method 1 and Method 2 are the same as above. The yield of method 1 was 65.84%, and method 2 was 41.06%. The reaction is shown in Figure 3.

![Fig. 3 Synthesis of cysteine salt of aspirin](image)

6. Characterization

The melting point of the salt sample was measured by a micro melting point apparatus. The melting point of the lysine aspirin sample prepared by the first method and the second method was 153.8-155.2 °C and 154.4-155.9 °C respectively. Respectively the melting point of the cysteine salt sample of aspirin was 188.6-191.2 °C and 187.2-191.5 °C.

Fourier-transform infrared spectrum (FT-IR) was collected on a Spectrum 100 (PerkinElmer) and then measured from 4000 to 500 cm⁻¹. Comparison: By comparing the peak shape and wavenumber of the standard (Fig. 4) and the infrared absorption spectrum of the sample (Fig. 5, 6), we can determine that the standard and the sample should be the same substance, lysine aspirin. By comparing the peak shape and wavenumber of the reactants (aspirin and cysteine, Fig. 7, 8) with the infrared absorption spectrum of the sample (Fig. 9, 10), we can determine the formation of a new substance, which may be the cysteine salt of aspirin.

![Fig. 4 Standard of lysine aspirin](image)
Fig. 5 Samples of lysine aspirin (Method 1)

Fig. 6 Samples of lysine aspirin (Method 2)

Fig. 7 Aspirin
HPLC conditions: column: C18 analytical column; mobile phase: methanol-water-glacial acetic acid (40:60:1) as the mobile phase; detection wavelength: 276nm; flow rate 1 mL/min; column temperature: 25 °C; injection volume 10μl. The number of theoretical plates is not less than 2000 [10] according to the peak of lysine aspirin. The results showed that both samples contained lysine aspirin, and the method 1 was better than the method 2, and the yield was high. (The authors did not find suitable chromatographic conditions to determine the cysteine salt of aspirin)
7. Conclusion
A comprehensive analysis of the melting point, infrared absorption spectrum and high performance liquid chromatogram of lysine samples (Method 1 and Method 2) can confirm that the reaction product is indeed lysine aspirin; I only measured two kinds of aspirin. The melting point and infrared
absorption spectra of the cysteine salt samples (Method 1 and Method 2), but no other conditions were explored to further determine whether the material was formed. The new method (especially Method 1) offers the possibility to expand the production route of lysine aspirin, and also provides new ideas for the preparation of similar new drugs.

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