Synthesis Process Improvement of Famciclovir Drug Substance

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Abstract: Famciclovir is a purine nucleoside oral prodrug, officially launched in 1993, mainly used in the treatment of herpes zoster. After taking Famciclovir, the deacetylated group is oxidized to form Penciclovir, which contacts with viral and bacterial in the human body to convert into Penciclovir Mitsubishi acid, thereby inhibiting the replication of viral DNA and achieving antiviral effects. With the continuous improvement of medical level, the synthesis process of Famciclovir drug substance is also constantly innovating and improving, especially in the field of green pharmaceutical technology. Based on this, the main focus of this study is on green pharmaceutical technology, using materials such as 2-amino-6-chloropurine and 3-bromopropan-1,1,1-tricarboxylic acid triethyl ester as raw materials. The synthesis process is used to measure Famciclovir, and the time parameters, reaction temperature, and other factors in the synthesis process are analyzed and optimized. The appropriate steps and processes in the entire process are pooled and optimized to ultimately improve the synthesis process. While ensuring its drug properties, the synthesis process is optimized to improve the reaction yield and reduce the use of organic solvents, thereby improving production efficiency and quality.

Keywords: Famciclovir; Drug substance; Synthesis process; Improvement

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1. Introduction

Famciclovir is an antiviral drug commonly used in the treatment of primary genital herpes and herpes zoster. Its chemical name is 2-amino-9-purine, and it is the second generation of open-loop nucleoside antiviral drugs. It was first launched in the UK and had antiviral effects. The duration of its drug action is longer and the oral bioavailability is higher. It is found from some clinical research results that Famciclovir is also effective in inhibiting the replication of hepatitis B virus [1]. At present, the synthesis of Famciclovir drug substance mainly requires raw materials such as 3-bromopropan-1,1,1-tricarboxylic acid triethyl ester, 2-amino-6-chloropurine, and light anhydrous potassium carbonate. After multiple synthesis reactions, Famciclovir is finally formed. The entire synthesis process is relatively cumbersome, with many reaction steps being cumbersome, and a large amount of organic solvent input is required, resulting in a large amount of waste liquid, greatly increasing the synthesis process and production costs. Therefore, analyzing and optimizing the synthesis process of Famciclovir raw materials can better improve the production quality and efficiency of Famciclovir, greatly reduce its production costs, and achieve better economic benefits while ensuring its drug properties.

2. Analysis of the Synthesis Process of Famciclovir Drug Substance

(1) Synthetic equipment and reagents

The selected synthetic reagents for this experiment are industrial grade 2-amino-6-chloropurine, self-made 3-bromopropan-1,1,1-tricarboxylic acid triethyl este with a purity of 98.6%, industrial grade light anhydrous

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potassium carbonate, analytical grade dimethyl formamide, industrial grade sodium methoxide and methanol, analytical grade sodium borohydride, industrial grade dichloromethane and toluene, analytical grade acetic anhydride, triethylamine, 4-dimethylaminopyridine, sodium carbonate, and industrial grade anhydrous ethanol, D5H5A 5% palladium carbon, high-purity hydrogen gas, nitrogen gas, industrial grade ethanol ethyl ester, and analytical grade n-hexane, etc. The equipment used include an electronic balance, an electronic constant speed stirrer, a multi-purpose vacuum pump for circulating water, a rotary evaporator, a low-temperature coolant circulation pump, a blowing drying oven, and so on.

(2) Synthetic method

1) In the synthesis process of 2-amino-6-chloro-9-(2,2-diethoxyhydroxybutyrate-4-yl) purine (5), 55 ml of dimethylformamide and 10 g of 2-amino-6-chloropurine were first added into a 250 ml reaction flask, stirred evenly, and then 12.2 g of light anhydrous potassium carbonate was added into the reaction flask. Then, 25 g of 3-bromopropan-1,1,1-tricarboxylic acid triethyl ester was added to it, and when the temperature rose to 65-75°C, stirring was carried out while waiting for its reaction. During the reaction, the reaction solution changed from the original earthy yellow to brownish red. After the reaction is completed, the temperature of the reagent in the reaction flask drops to 30°C. The filtrate is extracted and subjected to vacuum distillation treatment. After no fraction is present, an oily brownish red substance can be obtained, which is 2-amino-6-chloro-9-purine with a purity of 100%.

2) In the synthesis process of 2-amino-6-chloro-9-(2-ethoxycarbonyl ethyl butyrate-4-yl) purine, 63 ml of methanol was added into a 250 ml reaction flask, and the reagent was reacted according to the above steps. After obtaining a brownish red oily substance, it was stirred until the brownish red oily solution clarified. Then, 11.3 g of newly prepared sodium methoxide was added into it. The liquid in the reaction flask was reacted at room temperature for 2 hours to obtain a large amount of white solid. After the temperature was lowered to 0°C, it was stirred again to obtain the crystalline substance and subjected to filtration. During this process, a small amount of cold methanol was first used to rinse the filter cake. Then, drying was carried out by a blowing drying oven at 65°C to obtain 14.2 g of white solid powder with a purity of 73.5%.

3) Synthesis of 2-amino-6-9-(4-hydroxy-3-hydroxymethylbutyl) purine (3). Add 11.6 g of the synthesized white powder into a reaction flask, and add 80 ml of dichloromethane and 4.7 g of sodium borohydride, then thoroughly stir them. Then, slowly drip methanol into a constant pressure drip funnel until 25 ml of methanol is completely dropped. During the process of dripping methanol, the temperature should be controlled between 25-30°C and a chemical reaction should be carried out for 2 hours. Then, 10 ml of acetic acid should be added for quenching reaction. After no gas is present, a white solid is obtained. Then, 50 ml of toluene is added for stirring. After the solid is uniformly dispersed, filtration is carried out, and the wet substance is placed under a blowing drying oven at around 65°C for drying. Finally, a 100% white solid is obtained.

4) Synthesis treatment of 2-amino-6-chloro-9-(4-acetoxy-3-acetoxymethylbutyl) purine (2). Add 80 ml of dichloromethane to a 250 ml reaction flask, and then place the white solid obtained from processes 1, 2, and 3, as well as 0.39 g of 4-dimethylaminopyridine and 7.5 g of triethylamine, in the flask to start stirring at ambient temperature. Then, slowly drop 10.8 g of acetic anhydride into the flask for reaction, which will last for 2 hours. Then, add 96 ml of drinking water and wash and extract with 100 ml of 50% sodium carbonate solution. At this time, perform vacuum distillation treatment until there is no fraction, and then add 50 ml of 4de anhydrous ethanol for recrystallization. After that, place the white filter cake in a blowing drying oven at around 65°C for drying. Obtain 72.3% of 9.1 g white solid.

5) Synthesis treatment of Famciclovir (1). Add 7.5 g of the white solid obtained from the above synthesis into a high-pressure reactor, and then add 75 ml of ethyl acetate for stirring. Then, add 3.4 g of anhydrous sodium carbonate and 1.1 g 5% Pd/C. Close the reactor and perform three nitrogen gas replacements, with the pressure

controlled between 0.02 MPa and 0.03 MPa. Perform three hydrogen gas replacements between 0.02-0.03 MPa, followed by 0.3 MPa hydrogen gas replacement. The reaction occurs at a temperature of 50-60°C. If the reaction pressure is lower than 0.2 MPa, additional pressure treatment can be carried out. If the pressure remains balanced for about 1 hour, stamping treatment can no longer be carried out; After 1 hour, carry out the draining and filtration, followed by rinsing the filter cake with 15 ml of ethyl acetate, and then perform vacuum distillation of the filtrate to obtain a small amount of ethyl acetate. At this time, it is fused with 45 ml of n-hexane and stirred for 2 hours. After filtration, 20 ml of ethyl acetate can be recrystallized for filter cake treatment, resulting in about 6 g of Famciclovir, with a purity of 99.8% and a recovery rate of over 90%.

3. Analysis of the Synthesis Process Results of Famciclovir Drug Substance

(1) The influence of reaction temperature in synthesis process

The synthesis process of Famciclovir drug substance includes multiple steps such as fusion, decarboxylation, reduction, and esterification hydrogenation. The most important step is the formation of the N-9 main product and N-7 by-product ratio. Only by improving the selectivity of the N-9 main product and reducing the proportion of N-7 by-product can the reaction speed and efficiency be accelerated, laying a solid foundation for the later synthesis reaction. During the reaction of this step, it is necessary to pay special attention to the reaction temperature, as the change in reaction temperature will affect the entire reaction progress, as well as the N-7 by-product and the N-9 main product. For example, the ratio of 3-bromopropan-1,1,1-tricarboxylic acid triethyl ester:2-amino-6-chloropurine:light anhydrous potassium carbonate is 1.25:1:1.5. This reaction uses dimethylformamide as the solvent, and after 6 hours of reaction, temperature changes will have a significant impact on the overall reaction.

Under constant other reaction conditions, if the room temperature is relatively low, the reaction will become slower, but as the temperature continues to increase, the speed and efficiency of the reaction will be faster; If the raw materials start to gradually decrease, at a temperature of 55°C, after 6 hours of reaction, the remaining raw materials will be about 0.78%, and as the temperature increases, the raw materials will also gradually decrease, but the amount of reduction in raw materials will not be much. Mainly because higher temperature will make the activation energy of the reaction more significant and rapid, and microscopic particles can form huge collisions, making the reaction speed faster [2]. With the rapid increase of temperature, the reaction speed can also be faster. However, many raw materials in the reaction process cannot be fully converted into reaction products, and some of them will generate N-7 by-product. Moreover, the proportion of this product in the reaction will continue to increase as the temperature continues to rise. The proportion of N-9 main product will gradually decrease at a temperature of 65°C. Therefore, based on the remaining situation and selectivity analysis in the raw material reaction, a temperature of 55°C-65°C is the optimal temperature for the raw material reaction. At this temperature, not only can the reaction be completed smoothly, but also the proportion of the main product generated after the reaction can be ensured to reach a certain level.

(2) The effects of reaction solvents in the synthesis process

The effects of using different solvents during the synthesis process of Famciclovir drug substance are also different, as shown in Table 1. Under constant conditions, the final effect of using dimethyl formamide solvent will be much better, and its effect is similar to that of DMF. Mainly because both are polar non proton solvents with very good solubility, they better accelerate the synthesis reaction, and at very low solubility, the reaction speed is relatively slow; however, dimethyl sulfoxide has a very high boiling point and is difficult to recover after use. Considering all factors, dimethyl formamide is more effective.

Table 1 The effects of reaction solvents in the synthesis process

Solvent	Mass content of 2-amino-6-chloropurine (%)	Mass content of N-9 product (%)
Dimethyl formamide	0.44%	83.1%
Dimethyl sulfoxide	1.26%	79.85%
Acetone	61.87%	26.02%
Acetonitrile	49.2%	37.28%
Anhydrous ethanol	52.82%	26.02%
Methylbenzene	78.52%	18.45%

(3) The effects of reaction temperature on the production efficiency of Famciclovir in the synthesis process

As shown in Table 2, during the reaction process, if the reaction conditions remain unchanged but the temperature is different, the final formation of Famciclovir will also exhibit different situations. If the temperature is around 20°C, the reaction process will be greatly reduced, and after 6 hours of reaction, the residual rate of the raw material will be around 38.3%. However, as the temperature continues to rise and other reaction conditions remain unchanged, the residual rate of the raw material will decrease, and the content of Valacyclovir in the reaction solution will also continue to increase. When the temperature reaches around 60°C, the residual rate of the raw material will decrease to below 1%. At this time, the reaction effect at this temperature is relatively close, and the amount of impurities generated is also relatively small. From this, it can be concluded that the temperature of the synthesis process of Famciclovir drug substance can be set between 50°C and 60°C. This not only achieves certain reaction efficiency, but also reduces energy loss, ensuring the quality of Famciclovir.

Table 2 The effects of reaction temperature on the production of Famciclovir

Reaction temperature (°C)	Mass content of compound (2) (%)	Mass content of Famciclovir (%)
20	38.26%	61.34%
30	19.56%	80.01%
40	1.21%	98.0%
50	0.21%	99.22%
60	0.05%	99.5%
70	0.03%	99.5%

(4) The effects of hydrogen pressure on the production of Famciclovir

Hydrogen is a hydrogen-reduction raw material, and in the synthesis process of Famciclovir drug substance, the pressure of hydrogen will directly affect the production results. If the pressure is below 0.3 MPa, combined with the actual reaction situation, it is found that the raw materials cannot fully react. However, if the pressure is increased to 0.5 MPa, most of the raw materials will complete the reaction, and the residual rate of the raw materials will be below 0.1%. This also indicates that hydrogen pressure above 0.3 MPa will accelerate the synthesis efficiency and quality of Famciclovir drug substance. Therefore, it is best to control the hydrogen pressure between 0.3 and 0.4 MPa during the synthesis process of Famciclovir drug substance.

4. Conclusion

Through the analysis of the synthesis process of Famciclovir drug substance, it was found that the synthesis process of Famciclovir drug substance includes processes such as fusion, decarboxylation, reduction, esterification, and hydrogenation. After analysis, various parameters and key points in each process were adjusted and improved; especially the reaction parameters in each step were adjusted [3]. The results showed that if analyzed according to the weight ratio of the raw materials required for the synthesis of Famciclovir, the ratio of 3-bromopropan-1,1,1-tricarboxylic acid triethyl ester, 2-amino-6-chloropurine, and light anhydrous potassium carbonate was 1.25:1:1.5, and the most suitable temperature for the raw material reaction was between 55°C and 65°C; During the hydrogenation reduction process, the most suitable reaction temperature and hydrogenation pressure were found.

This also fully demonstrates that green chemical drug reaction technology can better optimize and improve the synthesis process of Famciclovir drug substance, which not only shortens the reaction time and efficiency, but also improves the production rate of Famciclovir, and improves its purity, greatly reducing the investment in organic solvents and production costs, and promoting the development of the synthesis process of Famciclovir drug substance.

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