Quality evaluation of synthesized modafinil used as pharmaceutical material

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ABSTRACT

Modafinil is a drug used in the treatment of narcolepsy, approved by the FDA in 1998. In previous studies, modafinil was easily synthesized through three stages, in the Bunte salt medium, the overall yield of 74,56 %. The quality of the modafinil was evaluated following USP 41. The results have shown that the synthesized modafinil satisfied quality requirements in pharmacopoeia.

Keywords: Modafinil; Smart drug; Bunte salt; USP.

1. INTRODUCTION

Modafinil belongs to the group of "smart drugs", manufactured by Cephalon Pharmaceutical Company and was approved by the FDA as a treatment for narcolepsy in 1998 [1]. Modafinil is able to replace amphetamine and methylphenidate, which have many disadvantages in tolerance and addiction when being used regularly. Many countries around the world have used modafinil in the military, with beneficial effects on the battlefield, including improving concentration, awareness of situations, controlling anxiety, reducing the need for sleep [1, 3].

The modafinil's mechanism of action is not clearly known, however, the action is involved in a wide range of release of substances, which are related to the action of nerve cells, including orexin, dopamine, histamine, norepinephrine, serotonin, γ-aminobutyric acid, and glutamate [4].

In previous studies, modafinil was easily synthesized by 3 steps in the Bunte salt medium, total efficiency reached 74,56 %. Product quality is evaluated according to the US Pharmacopeia (USP 41).

2. EXPERIMENTAL

2.1. Chemicals, instruments, research methods

2.1.1. Chemicals, instruments, equipment

Meeting the European Pharmacopoeia, standard modafinil was imported through chemical suppliers with a content of 99,9 % (CoA). Domestic standard salicylic acid was imported from the National Institute of Drug Quality Control with content of 99,9 %. Other chemicals are imported from Fischer company. Modafinil is synthesized in our own laboratory.

Instruments and equipment used in the experiment include HPLC Shimadzu high performance liquid chromatography (made in 2010, Japan), melting point apparatus STUART SMP3 (UK), IR Tensor II Brucker spectrometer (Germany), and some other common instruments.

2.1.2. Research methods

- Method of residue on ignition determination: as directed in USP 41, using concentrated sulfuric acid, quartz crucibles.

- Method of organic impurity determination: Determined by the high-performance liquid chromatography method, performed similarly to the quantitative method. The comparison of peak areas is carried out to give results of organic impurity determination.

- Method of water content determination: determined by the Karl Fischer titration method.

- Quantitative method: Quantified by HPLC liquid chromatography method, standard modafinil CRS with content of 99,9 %.

2.2. Quality evaluation of modafinil products

2.2.1. Identification evaluation method

Identification evaluation by IR spectroscopic method.

2.2.2. Quantitative evaluation method

- Buffer solution preparation: Completely dissolve 6.8 g of KH_2PO_4 in water. Adjust the pH to 2.3 with phosphoric acid.

- Mobile phase preparation: Prepare a mixture of acetonitrile and buffer solution at the ratio of 35:65 by volume.

- Dilution preparation: Prepare a mixture of solvent acetonitrile and water with a 35:65 ratio.

- Suitable systemic solution preparation: 5 µg/mL modafinil, USP and 10 µg/mL salicylic acid, USP in the diluent.

- Standard solution preparation: Completely dissolve 0.1 g of modafinil in 1 liter of diluent to obtain 0,1 mg/mL modafinil solution.

- Test solution preparation: Modafinil 0.1 mg/mL is diluted with the above prepared diluent.

- Chromatographic system: Detector: UV 220 nm; Column: size of 4.6 mm x 15 cm, 5 µm diameter; Column temperature: 40 ^oC; Flow rate: 1.0 mL/min; Injection volume: 15 µL.

- Systematic solution sample requirements: The relative retention times of modafinil and salicylic acid are 1.0 and 1.1, respectively.

- Suitability requirements: Resolution between modafinil and salicylic acid is not less than 1.3; tailing factor of modafinil peak is not greater than 1.5; The relative standard deviation of the modafinil peak is not much than 2.0 %.

- Procedure: Separately inject a sample of the test substance and a standard sample with an equivalent of approximately 15 µL into the liquid chromatograph, record the chromatogram and measure the main peak area.

- Calculate % modafinil ($C_{15}H_{15}NO_2S$) in the sample by the following formula:

$$\% \text{ Modafinil} = (r_U/r_S) \times (C_S/C_U) \times 100$$

Where, r_U is the peak response of the modafinil in the test sample;

r_S is the peak response of the modafinil in the standard sample;

C_S is the concentration of modafinil in the standard sample (mg/mL);

C_U is the concentration of modafinil in the test sample (mg/mL).

2.2.3. Evaluation of residue on ignition

- Heat 1 ceramic or platinum crucible at 600 °C ± 50 °C for 30 min, cool it down in a desiccator, then get from 1 to 2 g of the test sample in the crucible and weigh it.

- Moisten the sample with a small amount of sulfuric acid (R) (about 1 mL), then heat it at the slightest extent until the sample turns to ash completely.

- Cool down, moisten the resulting residue with a small amount of sulfuric acid (R), heat it up a bit until the white fumes are removed, and then heat it at 600 °C ± 50 °C until the residue completely turned to ash. While burning and heating prevent it from flaming.

- Cool the residue down in a desiccator and calculate its mass.

2.2.4. Evaluation of organic impurities

- Buffer solutions, mobile phase, test solution, suitable system solution and chromatographic

system are prepared as quantitative portions.

- Suitability requirements:

+ The resolution between modafinil and salicylic acid is not less than 1.3;

+ The tailed coefficient of modafinil peak is not much than 1.5;

+ The standard deviation of the modafinil peak is not much than 2.0 %.

- Procedure: Inject a sample of the reagent with a volume equivalent to about 15 µL into a liquid chromatograph, record the chromatogram and measure peak area.

- During the synthesis of modafinil, some impurities may appear in the product. The USP41 specifies the criteria for organic impurities in the table below.

Table 1. *Requirements for organic impurities.*

Name of impurities	Relative retention time (R_f)	Relative response factor (F)	Request, not much than (%)
Modafinil	1,0	-	-
Salicylic acid[a]	1,1	-	-
Modafinil acid[b]	1,4	1,0	0,5
Modafinil sulfone[c]	1,7	0,9	0,5
Modafinil ester[d]	3,0	1,0	0,5
Any individual unspecified impurity	-	1,0	0,05
Total impurities	-	-	1,0

- Impurities are determined by the formula: % Impurity = (r_U/r_T) x (1/F) x 100

Where, r_U is the peak response of each individual impurity;

r_T is the sum of the responses of all the peaks;

F is the relative response factor (see table 1).

2.2.5. Water content evaluation

- Reagent preparation: Prepare the Karl Fischer reagent as follows:

+ Add 125 g of iodine to a solution containing 670 mL methanol and 170 mL pyridine.

+ Put 100 mL of pyridine into a 250 mL measuring cylinder, cooling the outside of the cylinder with ice. Place the whole dry SO_2 in a volume of 100 mL. Add this mixture slowly to the cooled iodine mixture, while shaking it.

+ Shake until the iodine is dissolved, transfer the solution to the device, and leave the solution stand overnight before standardizing.

+ 1 mL of this freshly prepared solution is equivalent to about 5 mg of water, however it has been significantly degraded over time, so it should be standardized within 1 hour or daily if being used continuously. Store the reagent in a tightly closed container, protected from light, in a refrigerator.

- Test preparation:

+ Take the exact amount of sample containing from 2 mg to 250 mg of water. The water content depends on the water equivalence factor of the reagent and the method of endpoint determination.

- Reagent standardization: Transfer sufficient quantity of methanol or solvent to the titration vessel so that it is fully coated with the electrode and add a sufficient reagent to produce color change at the endpoint or 100 ± 10 µA current at 100 mV.

- Procedure:

+ Transfer the appropriate amount of methanol or solvent into the titration vessel, making sure the electrode is covered (about 30-40 mL).

+ Titrate with the reagent until the end point is observed.

+ Quickly add the test solution, mix and re-titrate with the reagent until an end point is observed.

- The smallest amount of test sample taken by the formula: F×C×V/K×F

Where, F is the equivalence factor of water in the reagent, mg/mL;

C is the usable volume of the burette capacity, %;

V is burette volume, mL; KF is the water content limit, %.

Calculate the water content in the sample, mg, using the following formula: S×F

Where, S is the volume of the reagent used in the second titration, mL;

F is the equivalent coefficient of water in the reagent.

3. RESULTS AND DISCUSSION

3.1. Standard modafinil sample CRS

Meeting the European Pharmacopoeia standard modafinil is imported by chemical suppliers with content of 99,9%. Molecular formula $C_{15}H_{15}NO_2S$, molecular weight 273,35 g/mol.

The quality performance indicator according to USP41 is shown in table 2.

Table 2. *Quality indicators of modafinil according to USP 41.*

Quality indicators	Requirement
1. Qualitative	The IR spectra of the test sample coincides with the standard sample
2. Quantitative, %	From 98,0 to 101,5
3. Residue on ignition, %, not much than	0,10
4. Organic impurities, %, not much than: - Modafinil acid - Modafinil sulfone - Modafinil ester - Other impurities which are not identified - Total impurities	 0,50 0,50 0,50 0,05 1,00
5. Water content, %, not greater	0,20

3.2. Quality evaluation of synthetic modafinil

3.2.1. Qualitative indicators evaluation

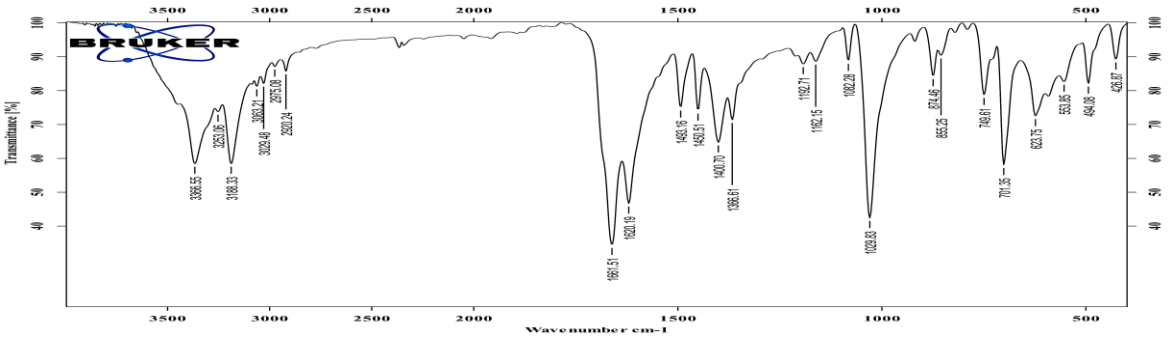

Figure 1. *IR spectrum of the synthesized modafinil sample.*

- On the IR spectrum appears absorption bands characteristic for the oscillation of the bonds present in the molecule, including: 3366, 3188 cm^{-1} (ν_{NH}), 3063, 3029 cm^{-1} ($\nu_{=CH}$), 2975, 2920

cm^{-1} (ν_{CH}), 1661 cm^{-1} ($\nu_{C=O}$), 1620 cm^{-1} (δ_{NH}), 1029 ($\nu_{S=O}$).

- The absorption bands appearing on the IR spectrum of the test sample perfectly match the absorption bands present on the reference sample.

3.2.2. Quantitative indicators evaluation

Quantitative evaluation is the most important criterion for evaluating the quality of a substance according to the pharmacopoeia. Calculate % modafinil ($C_{15}H_{15}NO_2S$) in the sample according to the formula:

$$\% \text{ Modafinil} = (r_U/r_S) \times (C_S/C_U) \times 100$$

The result shows that synthetic modafinil has a content of 99,2%, satisfying the quality criteria stated in the Pharmacopoeia (from 98,0 % to 101,5 %).

3.2.3. Evaluation of residue on ignition

- Residue on ignition or sulfate ash is a test to determine the content of non-volatile substances in a sample when the sample is heated in the presence of concentrated sulfuric acid according to the procedure given above. In essence, this test is used to determine the content of inorganic impurities in organic products. Residue on ignition can be affected by many factors, of which in particular inorganic impurities present in the product from the original material.

- Proceeding according to the procedure outlined above, the results showed that the residue content of the synthetic substance sample was 0,03 %. The residue on ignition is quite small, which is self-explanatory due to the high purity of the original chemical.

3.2.4. Criteria evaluation of organic impurities

Impurities can be classified into the following groups: Organic impurities, inorganic impurities and solvent residues.

Organic impurities may increase during product manufacturing and/or storage. Whether or not they are identified, volatile or non-volatile, they include original materials, by-products, intermediates, decomposition or reagents, ligands, and catalysts.

Results of organic impurities determination are presented in table 3.

Table 3. *Results of determining organic impurities in modafinil product.*

Name of impurity	**Retention time (minutes)**	**Peak area (mAu)**	**Impurity content (%)**
Modafinil acid	7,23	8,45039	0,02
Modafinil sulfone	8,52	4,22519	0,01
Modafinil ester	9,04	4,23892	0,01
Unidentified impurity	15,26	2,11260	0,005
Total impurities		19,02710	0,045

3.2.5. Water content evaluation

The water content in the sample should be determined to calculate the correct amount of active ingredients when preparing the final product.

This water quantification method is based on the total reaction of water with sulfur dioxide and iodine in an anhydrous solvent containing a suitable organic base. The common organic solvent is anhydrous methanol, sometimes replaced with another organic solvent suitable for dissolving the inoculant. The organic base is pyridine, but now other organic bases have been used instead, such as imidazole, 2-methyl-aminopyridine.

Test results show that the water content in the sample is 0,12 %.

4. CONCLUSION

In previous studies, modafinil has been synthesized in 3 stages; in the Bunte salt intermediate, total efficiency reached 74,56 %.

In this work, modafinil is evaluated for quality criteria according to the US Pharmacopeia (USP 41). The results showed that the content of modafinil in the sample reached 99,2 %, other indicators such as residue on ignition, impurities, and water content were all within limits specified by the Pharmacopoeia. Therefore, the modafinil product fully meets the quality criteria specified in USP 41.

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TÓM TẮT

Đánh giá chất lượng modafinil tổng hợp làm nguyên liệu dược

Modafinil là một loại thuốc được sử dụng trong điều trị chứng ngủ rũ, đã được FDA phê duyệt vào năm 1998. Trong những nghiên cứu trước đây, modafinil đã được tổng hợp dễ dàng qua 3 giai đoạn, thông qua chất trung gian muối Bunte, hiệu suất tổng cộng đạt 74,56 %. Bài báo này trình này kết quả đánh giá chất lượng của sản phẩm sau tổng hợp theo Dược điển USP 41. Kết quả cho thấy, sản phẩm modafnil đáp ứng đầy đủ các chỉ tiêu chất lượng theo USP 41.

Từ khóa: Modafinil; Thuốc thông minh; Muối Bunte; USP.