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The Influence Study of The Mole Ratio Reactant in Ceftriaxone Sodium Synthesis Against The Yield of The Production

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ABSTRACT

Ceftriaxone is one of the third generations of cephalosporin antibiotics and commercially found as a sodium salt. The market demand for it is still high in recent years, including in Indonesia. However, there is no local production manufacture yet. A high yield of ceftriaxone sodium would be an advantage in industrial scale. Ceftriaxone was synthesized by reacting 7–amino–3–[(2,5–dihydro–6–hydroxy–2–methyl–5–oxo–1,2,4–triazin–3–yl) thiomethyl] cephalosporanic acid (7-ACT) with 2-Mercaptobenzothiazolyl (Z)-2-(2-Aminothiazole-4-yl)-2-Methoxyimino Acetate (MAEM) then with sodium salt in basic condition. The product was generated by solventing-out using acetone. The products were analyzed by HPLC quantitatively and the structure was confirmed using FTIR, MS and NMR. In this research, the variation in the mole ratio of reactants against the yield of product was evaluated. The result showed that the variations in mole ratio reactants affect the yield production. The higher ratio of MAEM would be the higher yield is obtained. The results show that the yield was 72,17% at mole ratio 1:2 which has 99,32% purity. This result could be a consideration in industrial production scale in ceftriaxone sodium preparation.

Keywords—*ceftriaxone sodium; mole ratio; yield*

I. Introduction

Ceftriaxone has white to yellowish-orange odourless crystalline powder. It has obtained high status among the cephalosporin drugs. Like other third-generation cephalosporins, it is considerably less active than first-generation drugs against gram-positive bacteria but has a much broader spectrum of activity against gram-negative organisms. It is also effective against gram-negative anaerobes and Enterobacteriaceae (Echeria coli, Enterobacter, Klebsiella pneumoniae) [1].

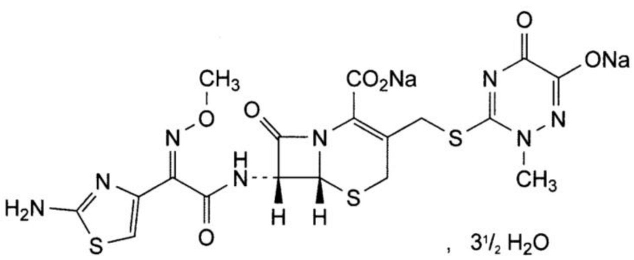


Fig. 1.Chemical structure of ceftriaxone disodium hemiheptahydrate [2]

Ceftriaxone is effective in the treatment of various infections caused by susceptible organisms including those of the bone and joint, abdomen, lower respiratory tract, meninges, pelvic area, skin and soft tissue, and the urinary tract. It is also effective in the treatment of septic arthritis, bacteremia, and gonorrhea, caused by organisms susceptible to the antibiotic [1, 3, 4].

Ceftriaxone sodium (Fig. 1) could be obtained by reacting 7-ACT with MAEM then the suspension reacts with sodium salts such as Sodium acetate, sodium carbonate and sodium 2-ethyl hexanoate.

The reaction between ceftriaxone and sodium salts occurred at the basic condition, pH ≤ 8. If the pH above 8, ceftriaxone sodium could be dissolved and it is disadvantage the process [1]. There are other methods to obtained ceftriaxone by substituted the starting material, 7-ACT substituted with 7-aminocephalosporanic acid (7-ACA) [1] or substituted MAEM with other Active esters [5]. However, these methods profitable less in step process which needs a lot of steps and supporting materials.

One of the factors to make a profitable industry is a high yield production. The yield production depends on the reaction process which is the reaction condition affects the yield. There are some factors in reaction; temperature, pressure, concentration, surface area and catalysts. Hence, this research has evaluated the variation in the mole ratio of reactants against the yield of the product. Increasing a mole ratio of reactant could accelerate the reaction rate at some typical reaction. The variation in the mole ratio of 7-ACT: MAEM is 1:1; 1:1.25; 1:1.5 and 1:2. The higher concentration of reactants could accelerate the reaction. Therefore, increasing 7-ACT would not favorable because the solubility characteristic as same as ceftriaxone sodium which it would be a matter to remove the excess 7-ACT. So, increasing concentration of MAEM could lead to a higher yield production.

II. Methodology

A. Materials

The chemicals that used in this research are purchased, MAEM and 7-ACT from Hefei Joye Import & Export Co., Ltd, China, Triethylamine and Sodium acetate trihydrate from Merck. The working standard is Ceftriaxone disodium hemiheptahydrate from Santa Cruz Biotechnology, Inc. for comparison.

B. Variables

There are 3 variables in this research. First, the independent variables was mole ratio of MAEM, 1; 1,25; 1,5; 2. Second, the dependent variables was the yield and the purity of the product. Third, the control variables was temperature reaction between MAEM, 7-ACT, and Triethylamine at 15°C, the other steps of the process at ambient pressure.

C. Methods

The method of ceftriaxone sodium synthesis in this research based on US Patent No. 5574155 in 1996, Example 1 [6] and used 1/10 reactants as a basis in the reaction. The amount of MAEM based on mole ratio was dissolved in the mixture distilled water and acetone in the Erlenmeyer flask 250 mL then 7-ACT was added. The Triethylamine solution was added to suspension and stirred at 15°C. Sodium acetate trihydrate was added to form a sodium salt of ceftriaxone. Acetone was added with rate 2 ml/min [7] and slow down the rate 1 ml/min to solventing-out the solid product from the solution. The products were centrifuged, washed by the mixture of distilled acetone and water [2,8] then dried in desiccator vacuum.

The synthesis product was analyzed by HPLC (UFLC Shimadzu 20A) to check the purity of the product in and the structure was confirmed by FTIR (Thermo Scientific, Nicolet iS10), proton NMR and MS spectra with ESI-positive ion method.

III. Results

A. The Qualitative Test Results

The product sample tested by FT-IR Spectroscopy, the results can be seen in Table 1 for similarity and Fig. 2.

Table 1. Similarity percentage of ceftriaxone sodium synthesis product

Ratio Mole 7-ACT	Ratio Mole MAEM	% Similarity
1	1	88,41
1	1,25	89,36

1	1,5	88,55
1	2	92,71
Working standard Santa Cruz		95,10

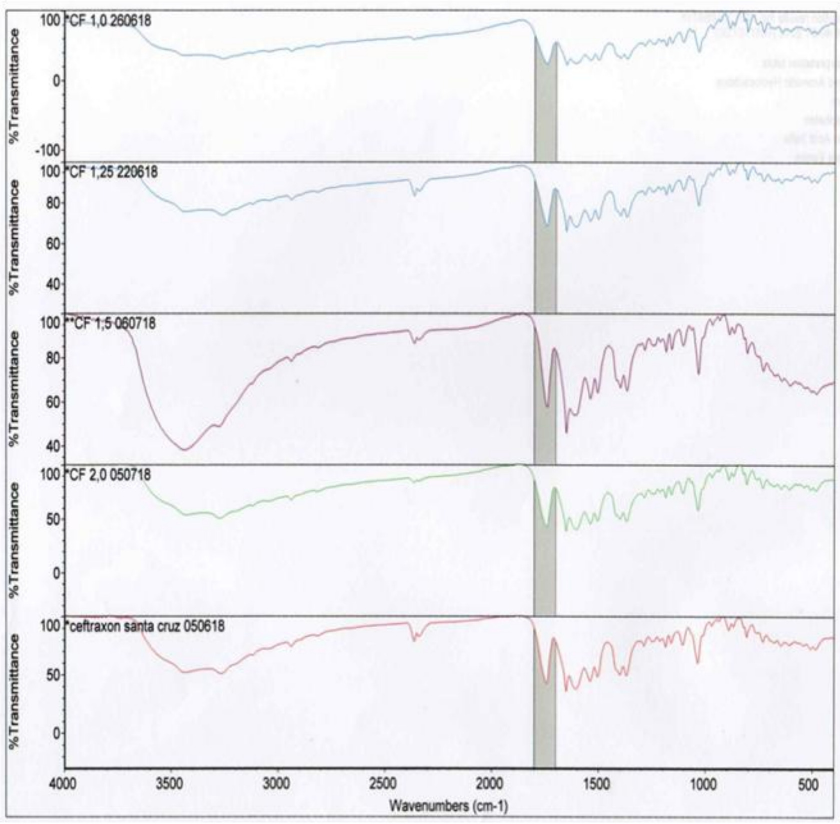


Fig. 2. IR-Spectra of the synthesis product and the RDS Santa Cruz

The product also tested by NMR and LC-MS. The results can be seen in Fig. 3 and Fig. 4. The qualitative test done for certainty the product is sodium ceftriaxone.

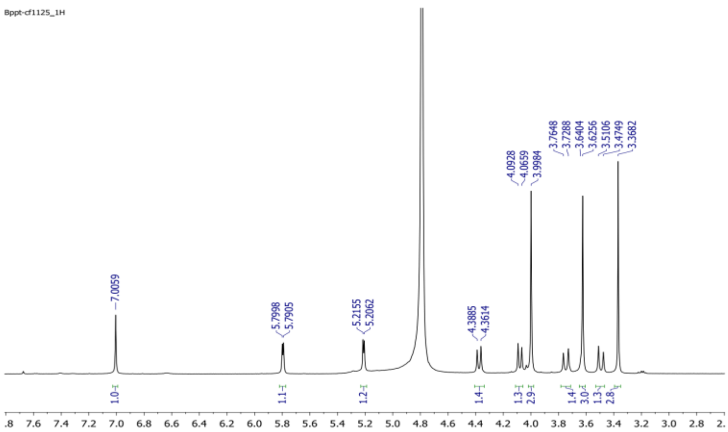


Fig. 3. 1H-NMR Spectrum of the synthesis product

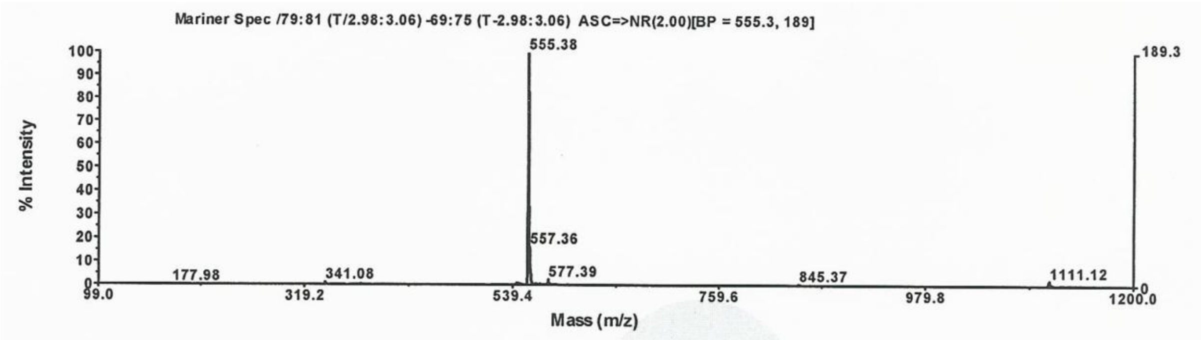


Fig. 4. LC-MS spectrum of synthesis product

B. The Quantitative Test Results

The synthesis products tested by HPLC to acquire the purities and calculated the yield.

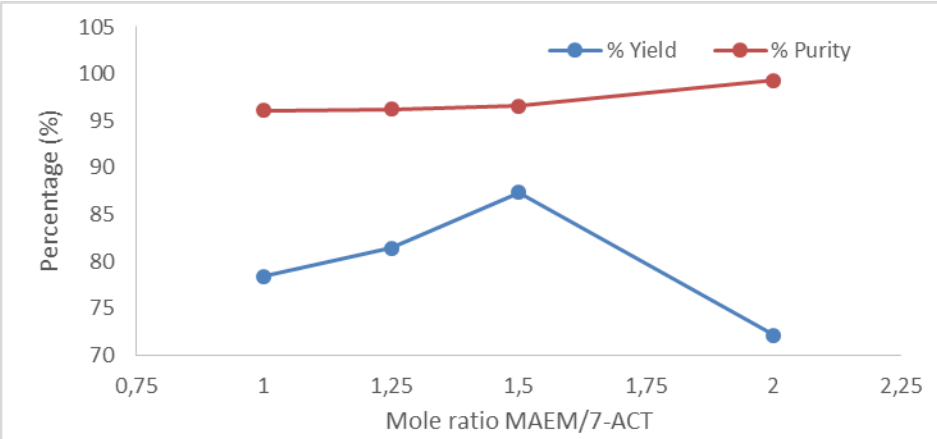
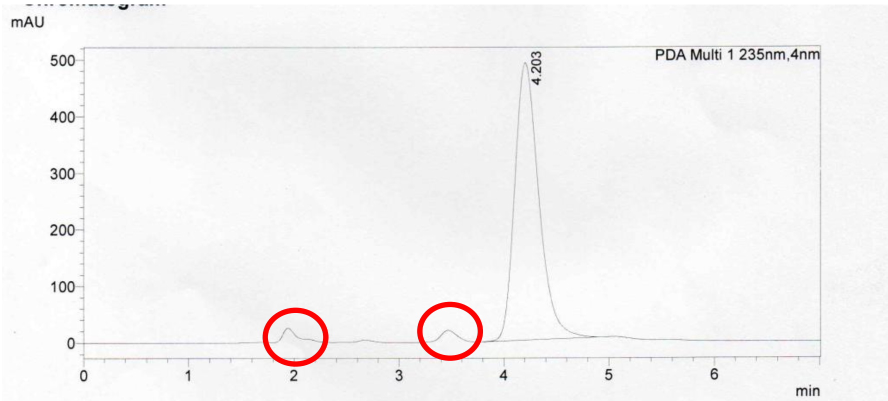


Fig. 5. The yield and purity of the synthesis product

The purity of working standard also tested by HPLC for a comparison with the sample products.



(Figure 3 chromatogram of RDS Santa Cruz)

IV. Discussion

A. The Qualitative Test Results

The sample product analyzed by FT-IR Spectroscopy to confirm the sample is ceftriaxone sodium. The IR Spectral of the variable samples and standard has compared. In the Table 1 can be seen that 1:2 in mole ratio has the highest similarity with the standard, 92,71%. It compared with the data in the system library HR Georgia State Forensic Drugs as ceftriaxone meanwhile the working standard Santa Cruz 95,10% in similarity.

Trindade (2017) reported that the carbonyl present in the region between 1800 and 1700 cm^{-1} is specific and useful in the determination of ceftriaxone sodium in powder for injection [9]. Fig. 4 showed the carbonyl band in the region between 1800 and 1700 cm^{-1} which indicated the sample was confirmed as ceftriaxone sodium.

The product was analyzed by ^{1}H-NMR and the spectrum data confirm the structure of ceftriaxone sodium. ^{1}H-NMR (500 MHz, C_3D6O, δ, ppm): 7.00 (s, 1H, aromatic C-H), 5.79-5.80 (d, 1H, J = 5.0 Hz), 5.20-5.21 (d, 1H, J = 5.0 Hz), 4.00 (s, 3H, NO-CH_3), 3.63 (s, 3H, N-CH_3), 3.37 (s, 2H, S-CH_2). Some of the spectra had shifted compared to Owens [1] and Dash cited in their report which could be caused by the impurities of the product. There were some protons did not show up completely such as NH_2 and NH. In addition, the CH_2 band could overlap with another CH_2 band because there was only one spectrum detected.

The product also analyzed by LC-MS with 5µL volume injection, 0.2 mL/min in flowrate, methanol mobile phase in C-8 (15 mm x 2 mm) collumn. The spectrum in Figure 4 indicated that the product is sodium ceftriaxone which ceftriaxone has 554.53 in molecular weight. The mass peak show at 555.38 m/z for M+H so that the molecular weight is 554.38 which is similar with molecular weight of ceftriaxone.

B. The Yield and Purity of The Product

The product from all variable in mole ratio has yellowish powder in appearance. The yield and the purity can be seen in Fig 2. The results showed that the yield increased then decreased to 70,12% at 1:2 in 7-ACT:MAEM mole ratio while the purity still increased, significantly at 1:2 in mole ratio. It might happen when added more reactant could increase the yield but at a certain point the excess reactant could inhibit the reaction or interfere the solventing-out process. Jagadale (2012) also had the same phenomenon, at the certain mole ratio, the yield product decreased because the excess reactant interferes in the separation process which made solubility increased [10].

The purity was analyzed by HPLC then compared the sample results with the standard from Santa Cruz. All of the synthesis product had more than 96% in purity which above the USP standard 79,5%. The chromatogram showed that the standard had more than one peak. So, the samples were compared to highest peak only then calculated by a single point of view. Shrestha (2013) reported that the ceftriaxone sodium standard only had one peak and the impurities showed up after a few treatment variables [11].

V. conclusion

Based on the results, the synthesis product is ceftriaxone sodium, confirmed by spectra FT-IR, spectrum H-NMR, and spectrum LC-MS. The yield of ceftriaxone sodium could be improved by increased a mole ratio of MAEM at certain point although the purity could still be increased by added more mole of MAEM.

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