

# RECOVERY OF METHYL ACETOACETATE FROM ANTIBIOTIC PRODUCTION PLANT'S WASTE STREAMS

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**Abstract** Chemical recovery of methyl acetoacetate from the amoxicillin plant's waste stream was investigated. In process of amoxicillin production for activation of amoxicillin molecule, hydrolysis takes place at final stage. As a result methyl acetoacetate is formed. Liquid-liquid extraction was employed for the recovery of methyl acetoacetate from the waste stream. Diluted alkaline solution was used as an extractive agent for the chemical extraction process. Extraction was carried out while the pH was adjusted to 9.5 by addition of alkaline solution. The extraction was repeated in three consecutive stages to enhance the process yield. Finally, distillation was carried out to remove the volatile compounds residues. Samples were taken from each stage of separation for GC analysis. The recovered methyl acetoacetate with purity of 93 % and yield of 75 % was obtained from extraction and distillation processes.

**Keywords** Amoxicillin Plant, Extraction Process, Methyl Acetoacetate, Alkaline Solution, Distillation

**چکیده** در این پژوهش بازیافت متیل استواستات از پساب حاصل از تولید آموکسی سیلین بررسی شده است. در فرایند تولید آموکسی سیلین برای فعال کردن مولکول آموکسی سیلین، در آخرین مرحله از هیدرولیز استفاده می شود. در نتیجه این عمل، متیل استواستات شکل می گیرد. برای بازیافت متیل استواستات از پساب آموکسی سیلین از استخراج مایع-مایع استفاده شد. محلول قلیایی رقیق به عنوان حلال استخراج در فرایند استخراج شیمیایی به کار رفت. عمل استخراج در حالی انجام گرفت که با افزودن محلول قلیایی pH به ۹/۵ رسید. برای افزایش بازده فرایند، عمل استخراج در سه مرحله متوالی انجام شد. در نهایت، برای حذف ترکیبات فرار تقطیر صورت گرفت. از هر مرحله فرایند استخراج نمونه ای گرفته شد و مورد آنالیز کروماتوگرافی گازی (GC) قرار گرفت. نتایج حاصل از آنالیز GC نشان داد که بازده فرایندهای استخراج و تقطیر شیمیایی برای بازیافت متیل استواستات از پساب ۷۵ درصد و خلوص آن ۹۳ درصد بوده است.

## 1. INTRODUCTION

Methyl acetoacetate is one of the most widely used esters, found in pharmaceutical and agricultural waste streams [1,2]. It is used as an amine protecting agent in the manufacturing of antibiotics and also for the preparation of synthetic sweeteners "Dane Salts" [1-4]. Dane salt is resulted from the reaction of phenylglycine with an alkyl acetoacetate, such as methyl or ethyl acetoacetate. It is the main chain for the synthesis of  $\beta$ -lactam, also it is an intermediate compound for production of

amoxicillin [3,4]. Methyl acetoacetate is extensively used for manufacture of insecticides, pesticides and herbicides [1].

In process of amoxicillin production hydrolysis is used at the final stage for the activation of amoxicillin. In the hydrolysis, side branch of the amoxicillin molecule, which is not activated, is debranched and methyl acetoacetate is easily separated from the amoxicillin molecule [4,7,8]. The hydrolysis is carried out with a diluted organic acid solution. Also an inorganic acid, such as diluted hydrochloric acid at a low temperature may

be used. The diluted acid solution creates two phases; organic and aqueous phases. The liberated methyl acetoacetate is found in the organic phase while the antibiotic has remained in the aqueous phase. Methyl acetoacetate is the by-product of the hydrolysis that is easily wasted along with numbers of organic solvents. [7-9]

The annual wastes for methyl acetoacetate and ethyl acetoacetate for an amoxicillin plant is projected to be 100 tones [1]. The remained oily residues after solvent recovery in antibiotic production process have to be disposed as schedule wastes or incinerated. Waste recovery process is needed for the revival of fine chemicals, prevention of environmental pollution and also for improving economical feasibility of the production plant. Waste stream mixture may contain hazardous compounds. If the chemicals are not recovered from the waste stream, disposal of the waste chemicals may cause major environmental pollution for antibiotic production. Recovery of the chemicals such as methyl acetoacetate from organic phase has positive impacts, to make the production process economically feasible.

Recently, Cabre and his coworkers [3] investigated about a chemical process to recover pivalic acid, as one of the organic compounds found in the antibiotic waste stream. They have found that normal distillation process decomposed methyl acetoacetate and the separation based on boiling points was not successful for the recovery of fine chemicals from the waste stream [3].

$\beta$ -lactam antibiotics (amoxicillin, ampicillin, cephalexin, cefadroxil, cefazolin and few more antibiotics) are among the most widely used pharmaceutical compounds. These semi-synthetic antibiotics correspond to 65 % of the ever rising worldwide production of antibiotics [5]. The antibiotic manufacturing plant demands cryogenic process (the process temperature remained almost at  $-30^{\circ}\text{C}$ ) and hazardous solvents such as methylene chloride are used for the protection/deprotection of side groups of the synthesized drugs. The process may generate great amount of non-biodegradable wastes [6]. Therefore, chemical synthesis is being replaced by modern enzymatic process. Enzymatic synthesis is an environmental friendly process for antibiotic production under mild reaction conditions (aqueous environment, neutral pH and moderate temperatures) [5,6]. Since the chemical synthesis

of the antibiotics has been highly criticized, the chemical process was replaced by enzymatic synthesis. Also, there are number of production plants around the world need special attention for the recovery of chemical wastes. There are no data available in the literature for handling the waste chemical recovery, most of findings are patented and the results are unique for the specific plant.

The purpose of the present research was to recover and reuse the methyl acetoacetate from the downstream wastes which was obtained from local antibiotic plant (Iran Antibiotic Company, Sari). The samples were analyzed and the organic chemicals were successfully separated and recovered by a novel technique of separation. Finally, most of the methyl acetoacetate was recovered by extraction process followed by distillation.

## 2. MATERIAL AND METHODS

The standard chemicals for analysis were supplied by Merck. The waste sample was obtained from the waste stream of local amoxicillin plant (Iran Antibiotic Company, Sari). Gas chromatograph (GC) equipped with capillary column TRB-G43 and FID detector, Varian, Model 3800 (U.S.A.), Rota vapor Laborota Model 4001 Heidolph (Germany) for distillation and pH meter Model MP 220 Mettler (Swiss) were used.

The waste stream obtained from local amoxicillin production plant consists of methyl acetoacetate, pivalic acid, N, N-dimethyl acetamide, 2-ethyl hexanoic acid, isopropyl alcohol and methylene chloride. At the first stage of separation, diluted alkaline solution was introduced to the mixture for extracting acid and amide compounds from the waste stream. Alkaline solution was added to the waste sample till the pH was adjusted at an optimum value of 9.5 [3]. A pH meter was used to monitor the pH changes. Addition of alkaline solution along with vigorous mixing enhanced the mass transfer process. As a result of extraction process, organic and aqueous phases were formed. Then, the mixture was poured into a separation funnel. After 10 minutes of settling, the solution was separated distinctly into organic and aqueous phases. Most of methyl acetoacetate was found in

the organic phase. Three consecutive stages of extraction were required to enhance the process efficiency and yield. In each stage of separation alkaline solution was added until the pH was adjusted to 9.5. Extraction processes were accomplished as explained earlier. At final stage, simple distillation was carried out to recover the volatile compounds such as methylene chloride. This process was accomplished in a Rota vapor.

Material balances were conducted in each stage of separation and the separated samples were analyzed by the GC equipped with FID detector and a 30m capillary column for the identification and quantitative analysis of the chemical compositions. The detector and injector temperatures were 240°C and 220°C, respectively. Temperature programming was planned to run GC. The column temperature was kept at 35°C for 5 minutes then it was increased to 40°C with a rate of 1°C/min. In the second stage of temperature programming, the oven temperature was increased to 230°C with a rate of 6°C/min. The carrier gas for GC was nitrogen with a flow rate of 30 ml/min. The GC was operated with software known as star-chromatography workstation. The run time for each sample was 41.67 min.

### 3. RESULTS AND DISCUSSION

The chemical composition of the supplied waste stream obtained from the antibiotic plant and the boiling points of the organic compounds are

summarized in Table 1. Since N, N-dimethyl acetamide, methyl acetoacetate and pivalic acid in the waste stream have close boiling points, simple distillation technique was unable to separate the chemicals exist in the waste stream [10-14]. Generally, for separating organic compounds with close boiling points extractive distillation is recommended [11,15-17]. In extractive distillation, the extractive agent must have higher boiling point than the key components in the mixture. Also the extractive agent must be relatively non-volatile [11,17-19]. Selection of a suitable extractive agent with such properties was difficult, because there were more than two compounds with different functional groups and close boiling points in the waste. Therefore, liquid-liquid extraction was used for separating all of the organic compounds. Recovery of methyl acetoacetate was implemented for the economical feasibility of the operating process. An extraction process was applied for the recovery of the chemicals. The extraction was based on separating all of the chemicals found in the plant waste stream.

Diluted alkaline solution was introduced into the waste sample for the solvent extraction of organic chemicals from the organic phase. A mild base solution (alkaline condition) as an extracting agent was used, while strong alkaline solution can hydrolyze methyl acetoacetate to acid and alcohol [2].

Three consecutive stages of extraction were performed for extracting acid residues, alcohol and the remaining amide. Table 2 shows the obtained chemical analysis of the aqueous and organic

TABLE 1. Chemical Composition of Waste Stream for Amoxicillin Plant.

Chemical Compounds	Boiling Point (°C) [9]	Weight Percent
Methylene Chloride (MCH)	39.8	39.227
N, N-Dimethyl Acetamide (DMAC)	166	5.509
Iso Propyl Alcohol (IPA)	82.3	4.635
Pivalic Acid (PIVA)	164	30.420
2-Ethyl Hexanoic Acid (2EHA)	226	0.657
Methyl Acetoacetate (MAA)	164	19.552

**TABLE 2. Chemical Analysis of the Aqueous and Organic Phases after Extraction with Alkaline Solution.**

Chemical Compound	Original Sample Weight Percent	Aqueous Phase Weight Percent	Organic Phase Weight Percent	Distribution Coefficient
First Stage of Extraction with Alkaline Solution				
Isopropyl Alcohol	4.635	9.136	4.125	2.214
Methylene Chloride	39.226	4.083	57.975	0.07
Pivalic Acid	30.420	77.815	0.566	137.216
Methyl Aceto-Acetate	19.552	1.366	31.775	0.043
N,N-Dimethyl Acetamide	5.510	6.823	5.550	1.229
2-Ethyl Hexanoic Acid	0.657	0.777	0.007	115.791
Sum.	100.000	100.000	100.000	
Second Stage of Extraction with Alkaline Solution				
Isopropyl Alcohol	4.125	30.24	1.814	16.673
Methylene Chloride	57.975	19.78	63.319	0.313
Pivalic Acid	0.566	1.95	0.301	6.606
Methyl Aceto-Acetate	31.775	21.25	31.363	0.677
N,N-Dimethyl Acetamide	5.550	26.78	3.147	8.511
2-Ethyl Hexanoic Acid	0.007	0.000	0.056	0
Sum.	100.000	100.00	100.000	
Third Stage of Extraction with Alkaline Solution				
Isopropyl Alcohol	1.814	25.230	0.836	30.168
Methylene Chloride	63.319	30.022	62.442	0.481
Pivalic Acid	0.301	4.245	0.027	157.211
Methyl Aceto-Acetate	31.363	25.888	34.618	0.748
N,N-Dimethyl Acetamide	3.147	14.615	2.040	7.163
2-Ethyl Hexanoic Acid	0.056	0.000	0.037	0
Sum.	100.000	100.000	100.000	

phases in each stage of separation. In the first stage of extraction the distribution coefficients ( $k$ ) for pivalic acid and methyl acetoacetate were 137.216 and 0.043, respectively.

The high distribution coefficient means that most of pivalic acid was transferred to aqueous phase while methyl acetoacetate was kept in the organic phase along with methylene chloride. In the second and third stages of extraction, most of methyl acetoacetate was extracted by the organic phase. Finally, to eliminate the low boiling point organic compounds such as methylene chloride, single stage distillation was implemented. Table 3 shows the chemical analysis of the distillate and residue of the distillation column. The final product with the purity of 93 % and the yield of 75 % was obtained. The yield calculation was based on the mass of methyl acetoacetate over its initial mass in the feedstock.

Figure 1 shows the distribution diagram of N, N-dimethyl acetamide. Data obtained from the three consecutive stages of separation lie above the diagonal ( $y=x$ ). The weight percents of the components in the raffinate and extract are shown by  $x$  and  $y$ , respectively. The distribution coefficient ( $k=y/x$ ) for this case is greater than unity. That means, N, N-dimethyl acetamide was effectively

extracted by the alkaline solution [12-15]. Also, Figure 2 depicts similar results for the extraction of isopropyl alcohol from the waste sample.

Figures 3 and 4 show the distribution diagrams for methylene chloride and methyl acetoacetate.

In these diagrams, distribution curves lie below the diagonal ( $y=x$ ) which show the low tendency of these two compounds to dissolve in the alkaline solution. Results showed that the alkaline solution was very efficient for the extraction of the organic acids, amide and alcohols found in the organic phase.

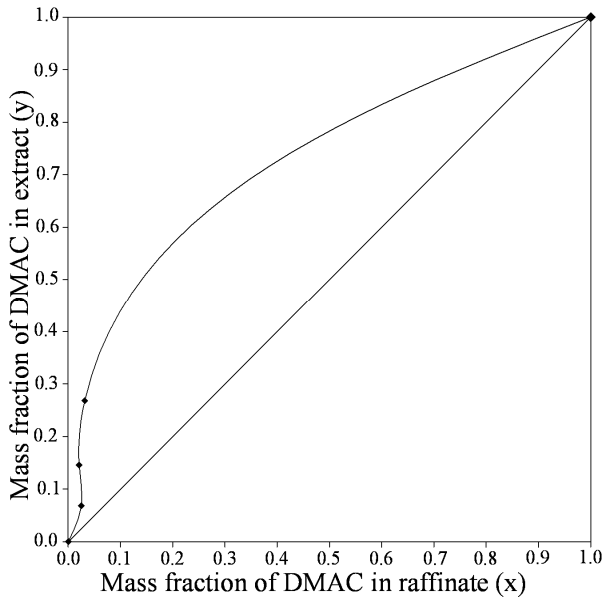
The recovered methyl acetoacetate can easily be converted to Dane salt, which is used in the preparation of the antibiotics. In addition, the recovered organic compounds are used as solvent for other industries. The use of alkaline solution as a novel solvent was not only to recover methyl acetoacetate but also for the extraction of pivalic acid from the waste stream.

#### 4. CONCLUSION

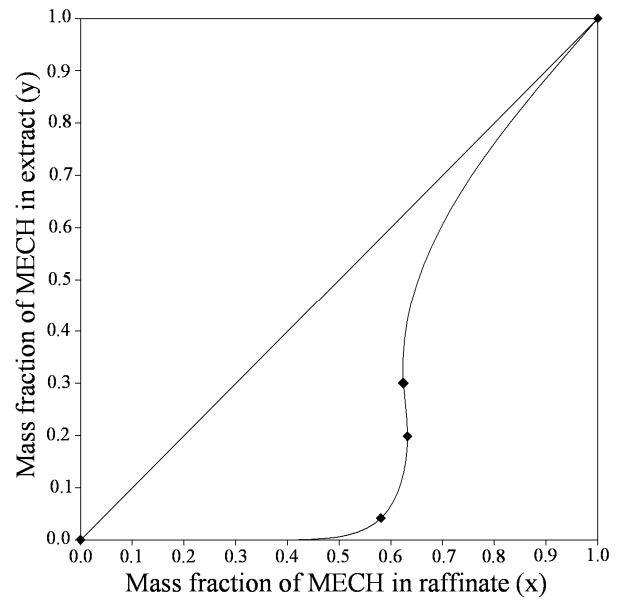
For waste stream processing of amoxicillin production plant, the chemical compounds such as

**TABLE 3. Chemical Analysis of the Distillate and Residue from Distillation Column.**

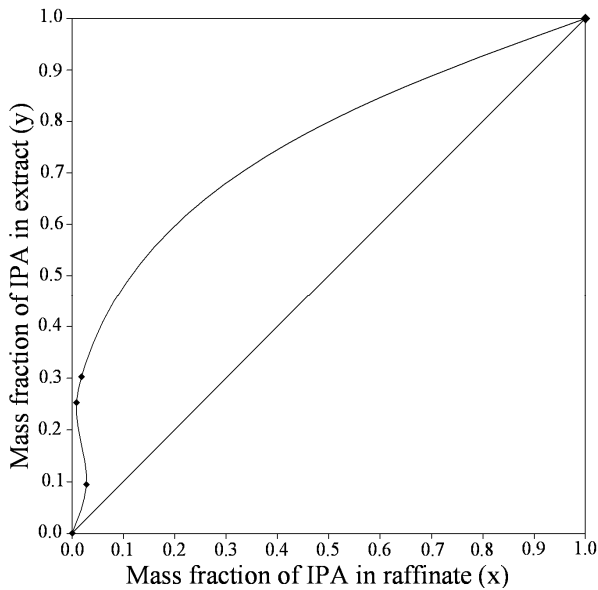
Chemical Compound	Original Sample Weight Percent	Weight Percent in Distillate	Weight Percent in Residue
Isopropyl Alcohol	0.836	2.468	0.017
Methylene Chloride	62.442	93.481	0.658
Pivalic Acid	0.027	0.000	0.000
Methyl Aceto-Acetate	34.618	3.806	93.818
N,N-Dimethyl Acetamide	2.040	0.245	5.507
2-Ethyl Hexanoic Acid	0.037	0.000	0.000
Sum.	100.000	100.000	100.000



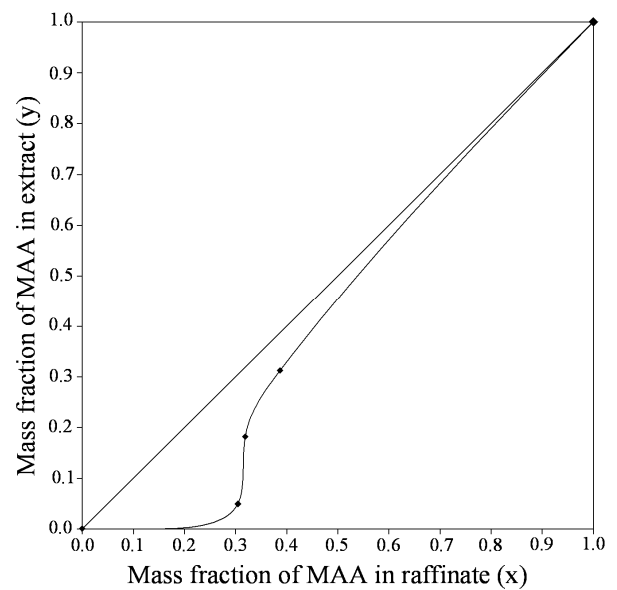
**Figure 1.** Distribution diagram for N, N-dimethyl acetamide.



**Figure 3.** Distribution diagram for methylene chloride.



**Figure 2.** Distribution diagram for isopropyl alcohol.



**Figure 4.** Distribution diagram for methyl acetoacetate.

methyl acetoacetate was recovered. The process set up was managed in a manner that most of the chemical compounds were extracted by addition of alkaline solution. Distillation was also applied at final stage. Results obtained from GC analysis

showed that alkaline solution was an effective chemical agent for the chemical extraction of the organic compounds found in the waste stream and the recovery of methyl acetoacetate was successfully achieved.

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