Process Intensification in Tiopronin Extraction

Zhigang Tang, Zhimin He, Hongwei Li, Dong Guo, and Zhijun Zhao

Abstract—In order to reduce the loss of ethyl acetate during tiopronin extraction, counter-current extraction is presented to replace the conventional cross-current extraction, as a process intensification strategy. Firstly the distribution coefficient of tiopronin between ethyl acetate and aqueous phase is determined. Next a calculation of counter-current extraction is done based on Matlab procedure. By the results, to achieve the effect of current production, it will save more than 60% extractant dosage by making use of 3-stage counter-current extraction. Moreover the conversion degree will increase three times replacing cross-current extraction by counter-current extraction.

Index Terms—Tiopronin, ethyl acetate, extraction, process intensification, conversion degree.

I. INTRODUCTION

Tiopronin (TPN), N-(2-thiol propionyl)-gly, CAS No 1953-02-2, is a new free thiol-containing glycine derivative. It can protect the liver tissue, improve liver function cells, repair ethanol-induced liver injury repair [1]-[7]. Schematic diagram of TPN industrial synthesis is shown as Fig. 1. Crude TPN got by reactions is then extracted by ethyl acetate (EA) from aqueous solution, evaporated and concentrated next. Finally, after crystallization and dry the product TPN is obtained.
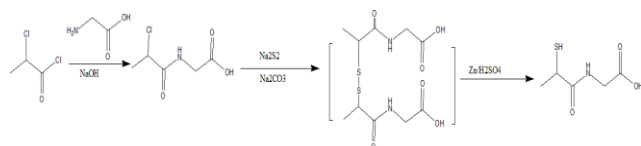

Fig. 1. Schematic diagram of TPN synthesis.

TPN is generally extracted by EA through 3-stage cross-current extraction. The fundamental process is as follows: 800~900 kg TPN aqueous solution (containing TPN 70~80kg) is put into the extraction tank 1 and mixed with 370~430kg EA at 151~20℃. Stirring for 30 min, mixture is settled and extract raffinate phase is separated from the extract phase. The raffinate from tank 1 is next mixed with 370~430kg EA in extraction tank 2 under the same conditions as in tank1 for 30 min. After clarification and phase separation, the raffinate from tank 2 is extracted repeatedly in tank 3 similar to tank 2 and tank1. Extract phase from tank1, 2, and 3 is collected to produce the TPN product after evaporation and crystallization.

The most serious problem puzzled this process is large loss of EA. According to factual data from workshop, the loss of EA is over than 30%.

After a primary analysis, except evaporative loss related to EA recovery, the important reason lead to large loss of EA is a large amount of EA used in low-efficiency cross-current extraction.

In this paper, counter-current extraction is presented to replace the existed cross-current extraction, in order to intensify the extraction of TPN, increase the conversion degree, reduce the amount of extractant and cut down the loss of EA.

II. EXPERIMENTAL

In order to compare the result of cross-current extraction with that of counter-current extraction, it needs to determine the distribution coefficient of TPN between organic phase and aqueous phase by experiments.

A. Materials

TPN (with purity of TPN ≥99%), TPN feed (aqueous solution, with conc. of TPN 10~20g/L), EA reagent (with analytic purity of EA ≥99.9%), EA extractant (with industrial purity of EA ≥99%), all is supplied by CONGQING KANGLE Pharmaceutical Co., China.

B. Procedures

(a) 1~10 g TPN is dissolved separately in 1000ml deionized water to prepare TPN aqueous solution with different concentration. TPN aqueous solution is mixed with EA reagent at different volume ratio, stirred for 30 min in a conical flask at room temperature. After phase separation, extract phase and raffinate phase is analyzed by HPLC and conc. of TPN in two phases is determined. Then distribution coefficient of TPN is calculated;

(b) TPN feed is firstly pre-treated by filtration to remove suspended solid, then is mixed with EA extractant at different volume ratio, stirred for 1hr in a conical flask at room temperature. After phase separation, extract phase and raffinate phase is analyzed by HPLC and conc. of TPN in two phases is determined. Distribution coefficient of TPN is then calculated.

C. Analysis Method

Conc. of TPN is determined by Shimazu reverse HPLC [8]-[10], ∅4.6 mm×150 mm C18 column is used (stationary phase: Phenomenex Aqua, 5μm) ∘ Gradient elution is applied using mixture of A (2.3 g/L phosphoric acid aqueous solution) with methanol at flow rate of 1.0 mL/min. Analysis conditions is as bellow: detecting wavelength 210 nm, temperature of column 40℃, injection volume 20μL.

Concentration of TPN is aqueous phase and organic phase is calculated using external standard method, according to the following formula:

$$c_X = \frac{c_R \cdot A_X}{A_R} \qquad (1)$$

where: c_R —concentration reference substance (TPN with high purity of 99.9%), g/L; A_R —peak area of conference substance; c_X —concentration of sample, g/L; A_X —peak area of sample.

III. CALCULATION

A. Extracting Effect of Cross-Current Extraction vs. that of Counter-Current Extraction

Applied the fundamental calculation methods of cross-current extraction and counter-current extraction [11] and Introduced the distribution coefficient from experimental, it is programmed and solved based on MATLAB. During the calculation, it is assumed EA and water is immiscible.

B. Conversion Degree of Cross-Current Extraction and Counter-Current Extraction

To further compare the difference between the efficiency of cross-current extraction and that of counter-current extraction in time and in space, conversion degree [12], revealing the efficiency of mass transfer unit in time and in space, is introduced to evaluate the performance of cross-current extraction and counter-current extraction.

IV. RESULTS AND DISCUSSION

A. Determination of Distribution Coefficient

TPN is dissolved in water to prepare the TPN aqueous solution with a concentration of 1~10g/L. Then EA is used to extract TPN from the above aqueous solution to determine the distribution coefficient of TPN between two phases. The experimental results are shown in Table I.

TABLE I: DISTRIBUTION COEFFICIENT OF TPN AT 26.4°C

Phase ratio(volume)	2:1	1:1	0.5:1
Extracting 1 times	1.87	1.81	1.92
Extracting 2 times	2.11	2.10	1.84
Extracting 3 times	1.77	2.13	1.97
Average value	1.92	2.01	1.91

Note: Data are from the extraction of TPN aqueous solution prepared by TPN dissolving in deionized water using EA reagent.

TABLE II: (A) DISTRIBUTION COEFFICIENT OF TPN AT 26.6°C BETWEEN RAFFINATE AND EXTRACT AFTER 1ST EXTRACTION

parameters	Raffinate after 1st extraction	Extract after 1st extraction
volume/mL	48.30	41.00
weight/g	58.80	34.60
Conc. of sample1 (g/L)	12.69	22.31
Conc. of sample1 (g/L)	12.48	21.94
Ave. Conc. (g/L)	12.59	22.13
Distribution coefficient	1.76	

As what we have seen, distribution coefficient of TPN, determined under experimental conditions as listed in section II, according to method (a) in B procedures, using EA reagent, from the extraction of TPN aqueous solution prepared by TPN dissolving in deionized water, nearly equals to constant, between 1.91~2.01.

According to method (b) in B procedures, TPN feed is firstly pre-treated by filtration to remove suspended solid, then is mixed with EA extractant. Distribution coefficient of TPN determined by experiments is shown in Table II.

TABLE II: (B) DISTRIBUTION COEFFICIENT OF TPN AT 26.6°C BETWEEN RAFFINATE AND EXTRACT AFTER 2ND EXTRACTION

parameters	Raffinate after 2st extraction	Extract after 2st extraction
volume/mL	44.60	40.40
weight/g	47.10	35.80
Conc. of sample1 (g/L)	7.10	12.56
Conc. of sample1 (g/L)	6.98	12.35
Ave. Conc. (g/L)	7.04	12.46
Distribution coefficient	1.77	

TABLE II: (C) DISTRIBUTION COEFFICIENT OF TPN AT 26.6°C BETWEEN RAFFINATE AND EXTRACT AFTER 3RD EXTRACTION

parameters	Raffinate after 3st extraction	Extract after 3st extraction
volume/mL	42.10	40.20
weight/g	50.60	35.10
Conc. of sample1 (g/L)	4.35	7.78
Conc. of sample1 (g/L)	4.28	7.65
Ave. Conc. (g/L)	4.32	7.72
Distribution coefficient	1.79	
Ave. distribution coefficient	1.77	

Note: 1.Data are from the extraction of TPN feed by EA extractant; 2.Ave conc. of TPN feed is 16.84 g/L; 3 Phase ratio (volume of TPN feed vs EA extractant) in extraction is 50:40.

As shown in Table II, distribution coefficient of TPN, determined under experimental conditions, according to method (b) in procedures B, from the extraction of TPN feed, also nearly equals to constant, between 1.76~1.79. But it is smaller than that from the extraction of TPN aqueous solution prepared by TPN dissolving in deionized water using EA reagent.

By primary analysis, decrease of distribution coefficient of TPN may be due to the impurities containing in TPN feed produced from synthesis of TPN. In industrial production, EA extractant is recovered and re-used repeatedly. This may lead to reduction of EA content in extractant and affect on extraction of TPN.
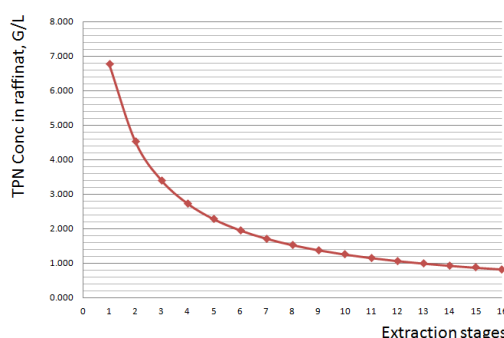
A. Calculation of Cross-Current Extraction and Counter-Current Extraction

Using MATLAB programming, calculation is done to simulate the multi-stage cross-current extraction and multi-stage counter-current extraction by experimental results. In calculation, coefficient of TPN between two phase is taken as 1.77. The concentration of TPN in feed and feed throughput is 13.5 g/L and 900kg/d, separately. According to factual production parameters, 1140 kg EA extractant was used evenly in 3-stage cross-current extraction, finally the concentration of TPN raffinate is about 3.4 g/L. Fig. 2 shows the change of concentration of

TPN in raffinate with the extraction stages in cross-current extraction and counter-current extraction, to reach the same TPN concentration in 3rd raffinate phase.
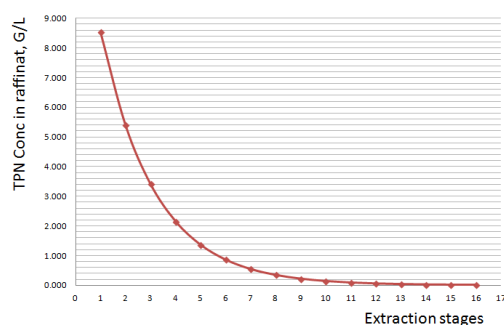
(a) In cross-current extraction with EA eatractant amount of 1140 kg.

(b) In counter-current extraction with EA extractant amount of 450 kg

Fig. 2. Change of TPN concentration in raffinate with the extraction stages in cross-current extraction and in counter-current extraction.

(a) counter-current extraction
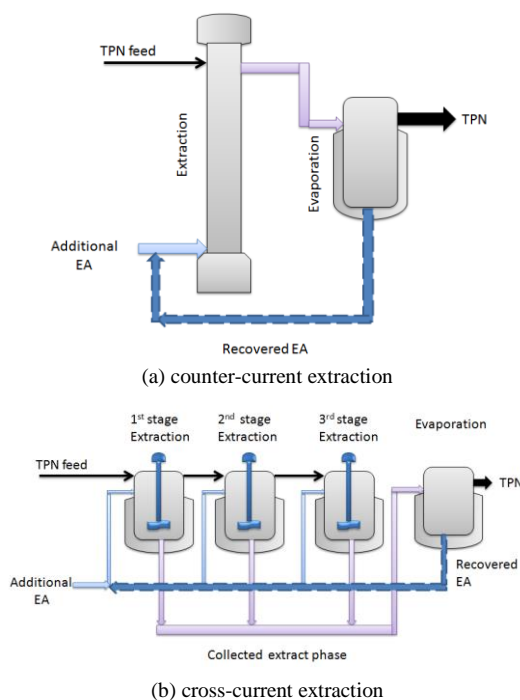

(b) cross-current extraction

Fig. 3. Schematic diagrams of counter-current extraction process and cross-current extraction process.

By the result, to reach the same TPN concentration 3.4 g/L in 3rd raffinate phase, equivalent to TPN recovery yield of 74.81%, it needs EA extractant 1140 kg in cross-current extraction but only 500 kg in counter-current extraction, all after 3-stage extraction. EA extractant can be saved more than by 60%. Moreover, if EA extractant amount is increased to 750 kg, TPN concentration in raffinate will decrease to 1.35g/L and TPN recovery yield is increased to

90%.

B. Conversion Degree of Cross-Current Extraction and Counter-Current Extraction

Counter-current extraction not only cuts down the amount and los of EA extractant but also simplifies the process, as shown in Fig. 3.

Moreover, counter-current can reduce the consumption, as shown in Table III.

TABLE III: DEVICE PARAMETERS AND CONSUMPTIONS FOR CROSS-CURRENT AND COUNTER-CURRENT EXTRACTION

Method	Cross-current extraction	Counter-current extraction
(1) Extraction parameters		
Recovered TPN	Average 75kg/d	Average 75kg/d
Total amount of EA extractant	1140kg/d	500kg/d
(2) Device parameters		
Extracting device	3m3×3	∅200×4500
Evaporating device	3m3	3m3
(3) Consumptions		
Loss of EA extractant	228kg/d	160kg/d
Electricity	30kw	10kw
Steam	0.74t/d	0.52t/d

In further illustrating the advantages of counter-current extraction in terms of space efficiency and time efficiency, a parameter of conversion degree [12] is introduced and calculated. Conversion degree is defined as the product yield within unit space volume, unit time and unit energy consumption. Authors have applied conversion degree to analyze the performance of several de-benzene process, such as double furnace-double column process, double furnace-single column process, single furnace-double column, single furnace-single column, respectively and achieved a good result.

According to Table III and definition the conversion degree of cross-current and counter-current is calculated as the following,

$$conversion \cdot \deg ree \cdot of \cdot cross - current \cdot extraction =$$

$$\frac{75kg/dTPN}{12m^3 \times (26.6 + 0.44 + 0.026)Mkcal/d} = 0.23kgTPN/(m^3 \cdot Mkcal) \quad (2)$$

$$conversion \cdot \deg ree \cdot of \cdot counter - current \cdot extraction = \quad (3)$$

$$\frac{75kg/dTPN}{(0.18 + 3)m^3 \times (21.3 + 0.27 + 0.008)Mkcal/d} = 1.01kgTPN/(m^3 \cdot Mkcal)$$

As can be seen, the conversion degree will increase dramatically when cross-current extraction is replaced by counter-current extraction.

V. CONCLUSIONS

During the experimental research range, distribution coefficient of TPN nearly equals to constant, between 1.91~2.01, when TPN aqueous solution prepared by TPN dissolving in deionized water is extracted by EA reagent; It also nearly equals to constant, between 1.76~1.79, when TPN feed is extracted by EA extractant. By MATLAB

programming and calculating, to reach the same TPN concentration 3.4 g/L in final raffinate phase, after 3-stage cross-current extraction and 3-stage counter-current extraction, the later can save EA extractant in amount more than 60% and When cross-current extraction is replaced by counter-current extraction, The conversion degree will increase by more than three times.

In further study, trial experiments will carry out to verify the performance of counter-current extraction of TPN.

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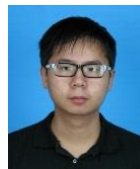
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