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Extraction of Hydrocortisone from the Fermentation Liquor with Annular Centrifugal Contactors

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Abstract: A continuous countercurrent extraction process for the recovery of hydrocortisone from the fermentation liquor has been developed with annular centrifugal contactors. When the hydrocortisone was extracted from the fermentation liquor with the butyl acetate, the distribution ratio increased with increase of the hydrocortisone concentration in the equilibrium aqueous phase. Both the laboratory tests and the plant tests have been finished with Φ20 mm and Φ230 mm annular centrifugal contactors respectively. In the laboratory tests, when the rotor speed was 3400 ∼ 4200 r/min, the fermentation liquor flow was 30 ∼ 50 mL/min and the phase ratio (V_O/V_A) was 0.36 ∼ 0.50, the percent recovery of hydrocortisone was higher than 92%. In the plant tests, when the rotor speed was 2000 r/min, the fermentation liquor flow was 2000 L/h and the butyl acetate flow was 1000 L/h, the percent recovery of hydrocortisone was about 96.5 ∼ 98%.

Keywords: Annular centrifugal contactor, hydrocortisone, countercurrent, extraction, butyl acetate

INTRODUCTION

Hydrocortisone is an important hormone drug usually used in the therapy for Addison's disease or chronic adrenocortical insufficiency as well as various skin

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disorders. In the pharmaceutical industry, a microbiological fermentation process is used to produce hydrocortisone, and then the solvent extraction method is used to extract hydrocortisone from the fermentation liquor with the butyl acetate (1, 2). At present, the crosscurrent extraction process is used to extract hydrocortisone with the butyl acetate extractant from the fermentation liquor in many pharmaceutical plants of China. The hydrocortisone production flowsheet is shown in Fig. 1 (3). The crosscurrent extraction process in the flowsheet consists of six stages of agitated tanks. So the high consumption of the butyl acetate extractant (the total phase ratio (V_O/V_A) is 0.7) and low recovery of hydrocortisone ($<90\%$) are the main drawbacks of the crosscurrent extraction process.

Annular centrifugal contactor is an efficient extraction equipment in solvent extraction processes. Compared with conventional contactors such as mixer-settler and pulsed column, the annular centrifugal contactor offers the following advantages (4, 5):

- low liquid inventories;
- excellent phase separation;
- high mass transfer efficiency;
- compact and short therefore low capital costs;
- do not lose the steady-state when shut-down;
- rapid start-up, shut-down and wash out of the process liquors.
- direct interconnection with any desired number of contactors for multi-stage processes.

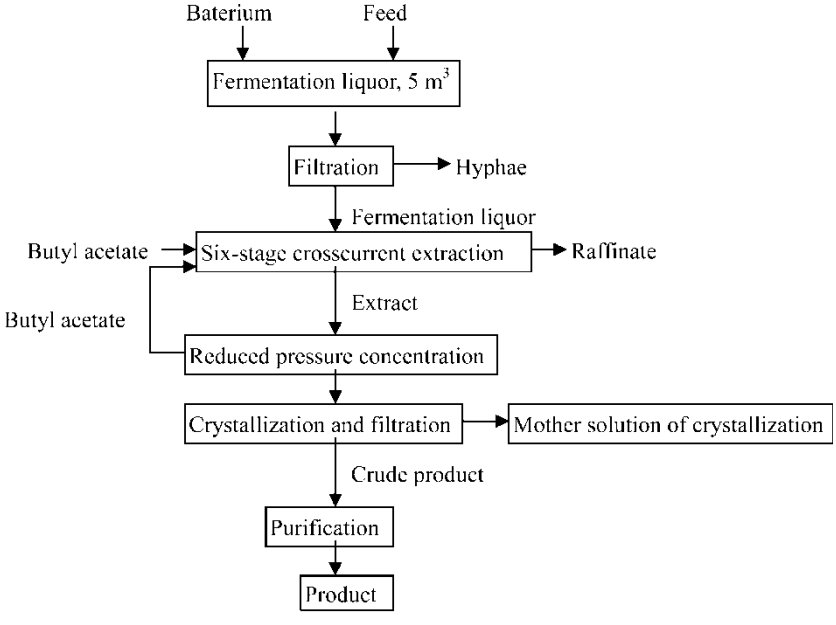

Figure 1. The current industrial process of hydrocortisone.

The primary centrifugal contactor was the paddle type. It had been successfully developed and operated for many years at the Savannah River Plant (SRL) in the United States. In the late 1960s, the paddle type centrifugal contactor was modified and an annular type centrifugal contactor was developed by the Argonne National Laboratory (ANL) USA. The ANL centrifugal contactor was reliable, easy to operate and maintain (6–8). In the late 1970s, the Institute of Nuclear and New Energy Technology (INET), Tsinghua University, China developed its own annular centrifugal contactors. A series of INET annular centrifugal contactors have been developed with the rotor diameter from 10 mm to 230 mm that have been successfully used in some industrial fields (9–12).

The objective of this work is to develop a continuous countercurrent extraction process to extract hydrocortisone from the fermentation liquor with annular centrifugal contactors.

EXPERIMENTAL

Materials

The fermentation liquor of hydrocortisone was obtained from the Dongbei Pharmaceutical Co. Ltd., China. The composition of the fermentation liquor is shown in Table 1. The butyl acetate used as the extractant was industrial grade and obtained from the Beijing Chemical Corp.

Apparatus

The annular centrifugal contactor operates as both separator and contactor because it's unique design providing mixing and separation in a single, compact unit. The schematic of annular centrifugal contactor is shown in Fig. 2. Two immiscible liquids with different density are fed from the opposite sides into the annular mixing zone between the spinning rotor and the stationary housing. The liquid-liquid dispersion created by turbulent Couette flow in the annular mixing zone flows by gravity to the inlet in the bottom face of the rotor and thus into the centrifugal separating zone inside

Table 1. The composition of the fermentation liquor (pH = 6.4–6.7)

Component	Hydrocortisone	Glucose	Corn syrup	Yeast	Ethanol	Ammonium sulfate
Concentration (g/L)	1.925–2.170	11.2	11.8	2.4	4.7–5.1	4.6

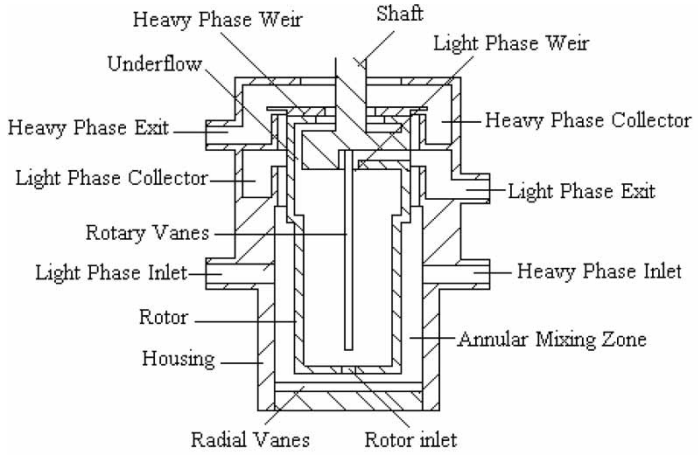

Figure 2. Schematic of the annular centrifugal contactor.

the rotor (4). Here the dispersion breaks and separates rapidly under the high centrifugal force. The two separated phases flow separately through the heavy phase weir and the light phase weir of the rotor into their collector rings in the housing. Then each liquid leaves its collector ring through a tangential exit, and flows into an adjacent contactor stage respectively. The extraction cascade is formed by linking its exits to the corresponding inlet of the neighbor contactors in the opposite direction.

Two types of annular centrifugal contactors used in the tests were designed and manufactured by INET, The one was ϕ20 mm annular centrifugal contactor (with the rotor diameter of 20 mm) used in the laboratory tests, and the other was ϕ230 mm annular centrifugal contactor (with the rotor diameter of 230 mm) used in the plant tests. The specifications of these two annular centrifugal contactors at the normal conditions are presented in Table 2.

Table 2. The specifications of annular centrifugal contactors

Type	ϕ20 mm	ϕ230 mm
Rotor diameter (mm)	20	230
Total flow rate (L/h)	0–5	0–6000
Hold-up volume of the liquids (mL)	19	12000
Flow ratio (A/O)	1/10–10/1	1/10–10/1
Suggested rotor speed (r/min)	3000–5000	2000
Stage efficiency	>90%	>90%
Entrainment (volume)	<0.5%	<0.5%

Procedures

It was reported that the temperature had no obvious effect on the extraction of hydrocortisone in the butyl acetate-fermentation liquor system over the range from 15 to 35°C (13). So, in our work, 25°C was chosen as the experimental temperature.

The mass transfer rate of hydrocortisone in the butyl acetate-fermentation liquor system was determined through the following process: 20.0 mL butyl acetate and 20.0 mL fermentation liquor were magnetically stirred for 5, 10, 20, 30, 60, and 90 seconds in a test tube respectively. Then the mixed two phases were separated by centrifugation and were analyzed by HPLC. In the extraction equilibrium tests, the fermentation liquor of hydrocortisone at fixed concentration was fully mixed with the butyl acetate at different volume ratios for 10 minutes, and then the mixed two phases were separated by centrifugation. The hydrocortisone concentration in the aqueous and organic phases was determined by HPLC. The distribution ratio was calculated as the hydrocortisone concentration in the organic phase divided by the hydrocortisone concentration in the aqueous phase at equilibrium.

In both the laboratory and the plant tests, the flowsheet of the cascade tests is shown in Fig. 3.

The recovery of hydrocortisone was calculated by the following equation from the inlet and outlet hydrocortisone concentration of the aqueous phase at steady state (14):

$$E = \frac{(C_{O,out} - C_{O,in})V_O}{C_{A,in}V_A} \times 100\% \quad (1)$$

where E was the percent recovery of hydrocortisone (%), V_A and V_O were the flow rate of the aqueous phase and the organic phase respectively (L/h), $C_{A,in}$ was the inlet concentration of hydrocortisone in the aqueous phase (g/L),

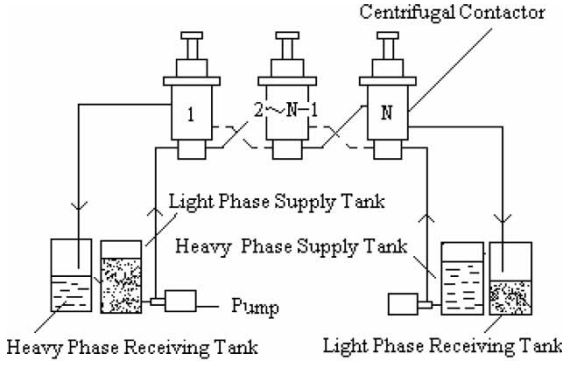

Figure 3. Flowsheet of the multi-stage cascade.

$C_{O,in}$ and $C_{O,out}$ were the inlet and the outlet concentrations of hydrocortisone in the organic phase respectively (g/L).

RESULTS AND DISCUSSION

Mass Transfer Rate of Hydrocortisone

Experimental results are presented in Table 3. It is shown that when the mixing time is more than 5 seconds, the hydrocortisone concentration in the organic phase does not change with the mixing time, and the extraction process reaches an equilibrium.

The mixing time of two phases in the annular centrifugal contactor is more than 5 seconds at the normal operating conditions. Moreover, the degree of mixing for two phases in the annular centrifugal contactor is much stronger than that in the test-tube. So, the annular centrifugal contactors can be used in extracting hydrocortisone with the butyl acetate from the fermentation liquor.

Distribution of Hydrocortisone in the Butyl Acetate-Fermentation Liquor System

The distribution ratio D of hydrocortisone in the butyl acetate-fermentation liquor system was determined. The results are shown in Figs. 4 and 5 (where $C_{A,eq}$ and $C_{O,eq}$ are the equilibrium concentrations of hydrocortisone in the aqueous phase and in the organic phase respectively (g/L)). The distribution ratio D was increased with increase of the hydrocortisone concentration in the aqueous phase. Xien Hu et al. had studied the extraction of steroid by-products in the fermentation liquor. The results showed that the distribution ratios of steroids between the butyl acetate and the fermentation liquor were less than that of hydrocortisone (2).

Table 3. Variation of the hydrocortisone concentration in the organic phase and the aqueous phase with the mixing time (25°C)

Mixing time (s)	5	10	20	30	60	90
Concentration in the organic phase (g/L)	1.811	1.809	1.811	1.811	1.815	1.813
Concentration in the aqueous phase (g/L)	0.336	0.338	0.342	0.336	0.338	0.340

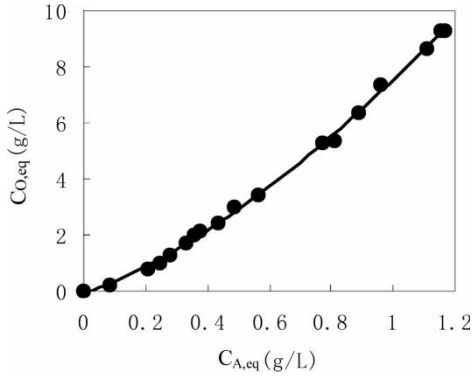

Figure 4. Distribution of hydrocortisone in the butyl acetate-fermentation liquor system at 25°C.

The total phase ratio (V_O/V_A) in the crossextraction process was 0.7 in the Dongbei Pharmaceutical Co. Ltd., China presently. In order to decrease the volume of the butyl acetate used in the extraction process of hydrocortisone from the fermentation liquor, the phase ratio (V_O/V_A) less than 0.5 was chosen in the tests. The calculated theoretical stage number was 6 for the continuous countercurrent extraction process of hydrocortisone when the phase ratio was 0.5.

The Laboratory Tests

Six ϕ20 mm annular centrifugal contactors were used to form the cascade system in the laboratory tests. The test conditions were that the rotor speed ω was $3400 \sim 4200$ r/min, the flow rate of the fermentation liquor was

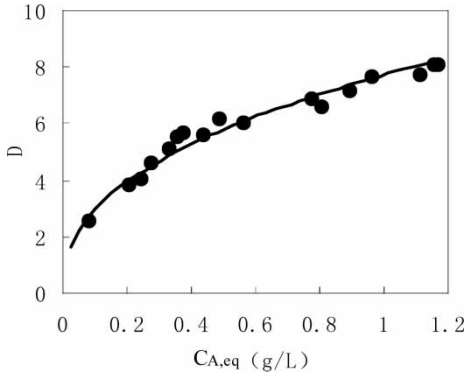

Figure 5. The distribution ratio of hydrocortisone in the butyl acetate-fermentation liquor system at 25°C.

Table 4. Results of the laboratory tests (25°C)

The phase ratio (V_O/V_A)	0.36 : 1	0.38 : 1	0.40 : 1	0.42 : 1	0.45 : 1	0.50 : 1
E (%)	92.35	92.20	93.04	93.16	94.05	95.21

$30 \sim 50\,mL/min$, and the phase ratio was $0.36 \sim 0.50$. The test results are shown in Table 4. The extraction recovery of hydrocortisone E was increased with the increase of the phase ratio in the laboratory test conditions. And the E was increased from 92.2% for the phase ratio of 0.36 to 95.2% for the phase ratio of 0.5. The recovery of hydrocortisone E was higher than that of 90% in the crosscurrent extraction process with the agitated tank in the Dongbei Pharmaceutical Co. Ltd., China.

The Plant Tests

The plant tests were carried out in the Dongbei Pharmaceutical Co. Ltd., China. In order to improve the recovery E, eight ϕ230 mm annular centrifugal contactors were used to form the cascade system in the plant tests. The test parameters were that ω was 2000 r/min, the butyl acetate flow was 1000 L/h, and the fermentation liquor flow was 2000 L/h (with the phase ratio of 0.5). The recovery E of hydrocortisone in the plant tests was about 96.5%–98%. However, the E of hydrocortisones was only about 88%–90% when the total phase ratio (V_O/V_A) was 0.7 for the crosscurrent extraction process with the agitated tank in the Dongbei Pharmaceutical Co. Ltd., China.

In addition, when contamination happened during fermentation, the concentration of hydrocortisone in the fermentation liquor was greatly decreased, and the mixture of both the fermentation liquor and the butyl acetate was easy to emulsify during extraction. It was difficult to separate emulsion by the gravitational separation method, so no hydrocortisone could be recovered by the crosscurrent extraction process with the agitated tanks from 5000 L of the contaminated fermentation liquor. However, the emulsion could be separated by annular centrifugal contactors because of centrifugal force, so about 2.5 kg of hydrocortisone could be recovered by the countercurrent extraction process with annular centrifugal contactors from 5000 L of the contaminated fermentation liquor.

CONCLUSIONS

Hydrocortisone in the fermentation liquor can be extracted with the butyl acetate. When the mixing time is more than 5 seconds the extraction process reaches its equilibrium. The distribution ratio is increased with increase of the hydrocortisone concentration in the equilibrium aqueous phase.

Annular centrifugal contactors have many obvious advantages. The continuous countercurrent process for the extraction of hydrocortisone from the fermentation liquor has been developed with annular centrifugal contactors. Both the laboratory tests and the plant tests have been carried out with ϕ20 mm and ϕ230 mm annular centrifugal contactors respectively. The tests were successful. The results showed high extraction recovery of hydrocortisone from the fermentation liquor could be obtained with annular centrifugal contactors.

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