The kinetics of erythromycin fermentation in an air-lift bioreactor

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Abstract: The kinetics of erythromycin fermentation in an air-lift bioreactor was studied. According to the kinetic equations, feeding strategies, the optimum process control parameters, the ratio of C/N (carbon/nitrogen) and oxygen uptake rates were obtained. It resulted in a significant improvement on the erythromycin fermentation. The total metabolic phase was reduced by 13% and the production was 10% higher than that by the traditional process.

Key words: erythromycin fermentation; process control; kinetics

CLC number: TQ92 **Document code**: A **Article ID**: 1000-274 X (2003)01-0034-03

Erythromycin fermentation was a process of fermentation with a high power consumption, large workforce, few technological parameters control and little information of parameters variation got from the process, resulting in a high fermentation costs. The fermentation process time was more than 160 hours and with low repeatability. Further, feeding process make it more complicated, so it was difficult to get reliable parameter values from it. Many ways have been used to improve it. It is easy to make a protocol but it is very difficult to execute it[1,2]. Many processes and engineering parameters affected biomass during the fermentation of erythromycin, the precursor, the substrate consumption during the different cell growth phases, the metabolic phase and the different type of bioreactor affected the formation of erythromycin[3]. It addresses on the analysis of fermentation kinetics to reach the optimum control of fermentation process according to the kinetics.

1 Material and Methods

1.1 Material

1.1.1 Strain *Streptomyces erythreus* (by Xi'an pharmaceutical factory).

1.1.2 Media corn starch, soybean, corn steep, yeast abstracts, $(NH_4)_2SO_4$, glucose, $CaCO_3$.

1.2 Methods

1.2.1 The first class seed cultivation 500 mL shake flask, for 72 hours at 33℃.

1.2.2 The second seed cultivation 500 mL shake flask, for 48 hours at 33℃.

1.2.3 The third fermentation Scale: 10 L, made in Bioengineering Company, Switzerland.

2 Analysis

2.1 The analysis of the substrate consumption of glucose and the total of N source

It is according to the analysis method of erythromycin fermentation of Xi'an Pharmaceutical

Received date: 2001-10-09

Foundation item: This project was supported by National Nature Science (29706007)

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Factory.

2.2 The analysis of product

the formation of the erythromycin is measured by the method of erythromycin fermentation of Xi'an Pharmaceutical Factory.

2.3 The biomass concentration

For the fermentation media containing a lots of unsolved materials, it is difficult to measure the biomass accurately, the method adopted is the packed-cell volume method[4].

3 Results and kinetics

3.1 The data source

Fermentation experiments were done in a series selected protocol. All useful data were got from the processes with a high final production concentration.

3.2 Model of kinetics

By the method of Highshide E.[5], the following equation were concluded.

3.2.1 The formation of erythromycin concentration (titer)

$$F(t) = 8.54 \times 10^{-2} t^2 + 18.47\, t - 728.26, \quad (t = 40 \sim 158\ \text{h}).$$

3.2.2 The variation of biomass

$$F(t) = -15\,495.293\, t/(3\,503.158 + t) + 82.787t/(27.183 + t) + 3.941\, t, \quad (t = 25 \sim 158\ \text{h}).$$

3.2.3 The glucose's consumption

$$F(t) = 0.936 + 4.584 \cdot \exp(-(t + 4.561)/25.898), \quad (t = 0 \sim 45\ \text{h}).$$

$$F(t) = 0.936 + 4.584 \cdot \exp(-(t + 4.561)/25.898), \quad (t = 45 \sim 80\ \text{h}).$$

$$F(t) = 0.936, \quad (t = 80 \sim 158\ \text{h}).$$

3.2.4 The variation of carbohydrate

$$F(t) = 0.936 + 4.584 \cdot \exp(-(t - 6.448)/17.812), \quad (t = 20 \sim 45\ h).$$

$$F(t) = 2.921 + 8.939 \cdot \exp(-(t - 6.448)/17.812), \quad (t = 45 \sim 80\ h).$$

$$F(t) = 2.921, \quad (t = 80 \sim 158\ h).$$

3.2.5 The variation of N-substrate consumption

$$F(t) = 37.232 + 45.150 \cdot \exp(-(t - 15.173)/5.327, \quad (t = 20 \sim 45\ \text{h}).$$

$$F(t) = 37.232, \quad (t = 45 \sim 158\ \text{h}).$$

4 The conclusion from kinetics

From the above mode of kinetics, the following information could be obtained:

1) When $t \to \infty$, the $F(t)$ value approaches constant. The analysis of above kinetics shows the results of metabolic control points as follows. The glucose concentration should keep 0.94%; the total carbohydrate concentration should be 2.92 % in broth; the N (nitrogen) substrate concentration should be 37.23 mg/mL in broth during the stage of erythromycin formation.

According to the equation of kinetics, the glucose concentration should be in the range of 1.2~1.5% during the cell log phase growth (20~45 h), the total carbohydrate concentration should reach 3.0% around and the N(nitrogen) substrate concentration should be 70 around (at least 40 above).

2) It is not a complicated mode of fermentation but useful to choose the original process control parameters, get effective control points and save a lots of time.

3) Under the guide of this mode and feeding strategy adapted and according to the data from the process of fermentation, the fermentation cycle decreased by 13% and the production formation rate got a 10% higher than that by traditional process.

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(编 辑 姚 远)

气升式生物反应器内红霉素发酵的动力学分析

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摘要: 研究了气升式生物反应器内红霉素发酵的动力学行为, 根据所归纳出的动力学方程, 调整发酵过程中的补料策略, 得出了比较优化的工艺和工程参数, 如发酵液的C/N(碳源/氮源)比、氧摄取速度(OUR)等。根据此动力学模型, 调整的优化发酵工艺使得菌体代谢周期缩短了13%, 而红霉素发酵水平提高了10%。

关 键 词: 红霉素发酵; 工艺控制; 动力学分析

·学术动态·

大陆动力学实验室进入省部共建实验室行列

近日, 国家科技部公布了全国首批省部(科技部)共建实验室名单, 此次共有9省区的9个地方重点实验室进入省部共建实验室行列。科技部年内将首批向这些实验室各投入90万元, 作为科研条件工作经费, 用于仪器购置、现有仪器配套软硬件、仪器改造、仪器研制等。我校的陕西省大陆动力学重点实验室入选其中, 这是大陆动力学实验室继2000年进入教育部重点实验室的又一发展良机, 从而为进入国家重点实验室行列迈出了重要一步。

省部共建实验室工作是科技部为了落实《2002年加强地方科技工作要点》, 根据《关于加强地方实验室工作的若干意见》精神, 进一步完善国家实验室体系, 推动地方实验室工作, 加强优秀地方实验室重点培育的重要举措。此次遴选的9个实验室都是受地方长期重视、与地方经济发展紧密联系、提供重大关键技术支撑的优秀地方实验室, 未来几年这些实验室将由科技部和地方以省部共建形式共同支持, 通过典型示范和引导, 提高地方实验室的整体水平。

(薛 鲍)