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Improving mass transfer efficiency for penicillin production by using a continuous stirred tank reactor: a review

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ABSTRACT

Continuous stirred tank reactors (CSTRs) play a pivotal role in the industrial production of chemicals, including antibiotics such as penicillin, due to their ability to enhance mass transfer efficiency. The CSTR's design facilitates precise control over aeration and agitation; two critical parameters that influence the volumetric mass transfer coefficient. Aeration supports cellular metabolism by supplying oxygen, while agitation promotes the dispersion of gas bubbles, thereby improving phase contact. This review explores the historical development of penicillin, its mechanism of action, the principles underlying bioreactor operation, and the specific ways in which aeration and agitation affect mass transfer dynamics. By optimizing reactor configuration, operating conditions, and associated process parameters, producers can significantly enhance the efficiency of penicillin biosynthesis.

1. Introduction

Since Alexander Fleming's discovery that certain *Penicillium* fungi produce penicillin, β-lactam antibiotics have significantly impacted global public health and quality of life. These fungi belong to a broader class of microorganisms capable of synthesizing antibiotic compounds that either kill competing microorganisms or inhibit their growth. In 2021, global expenditure on antibiotics reached $40.70 billion; a figure projected to rise to $61.29 billion by 2029[1]. This increasing demand underscores the need to enhance antibiotic production. The present review discusses the discovery of penicillin, its mechanism of action, and the role of aeration and agitation in optimizing its yield.

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2. History of penicillin

Penicillin, an antibiotic produced by the fungus *Penicillium chrysogenum*, is widely used in the treatment of bacterial infections. Chemically, it comprises a six-aminopenicillanic acid nucleus – a fusion of a β-lactam ring and a thiazolidine ring – with various cyclic side chains. In 1928, Fleming serendipitously observed that a culture of *Staphylococcus aureus* at St. Mary's Hospital in London had been contaminated by a *Penicillium* species[2]. The fungus secreted a substance that inhibited bacterial growth, which Fleming named "penicillin". Initially sceptical of its therapeutic potential in living organisms, Fleming did not pursue its clinical use. It was not until 1945 that a team from Oxford University – comprising Ernst Chain, Norman Heatley, and Howard Florey – successfully demonstrated penicillin's efficacy through clinical trials.

3. Mechanism of action of penicillin

Bacterial cells are typically enclosed by a peptidoglycan cell wall, which provides mechanical stability and prevents osmotic lysis. During growth and division, this structure undergoes continuous remodelling. Penicillin disrupts the biosynthesis of the peptidoglycan layer by irreversibly inhibiting transpeptidation. It binds covalently to penicillin-binding proteins, including the enzyme DD-transpeptidase, which catalyses the cross-linking of the peptidoglycan chains[3]. The strained β-lactam ring of penicillin facilitates this interaction, rendering the enzyme inactive. As a result, the bacterial cell cannot maintain its structural integrity, leading to cell death.

4. Penicillin production

Following the initial discovery, Fleming produced penicillin in shallow petri dishes (1- to 2-cm thick), yielding only minute quantities[4]. These limited yields posed challenges for the Oxford team's therapeutic trials, which coincided with the onset of World War II. Faced with the urgency of treating infected war wounds, the team developed a scalable production method. They engineered a compact, space-efficient vessel that offered optimal conditions for fungal growth and significantly increased penicillin output. This apparatus known as a "bioreactor" or "fermenter" was foundational to modern large-scale antibiotic manufacturing.

5. Bioreactors

Bioreactors are specialized cylindrical vessels engineered so as to create optimal conditions for the microbial fermentation required to produce desired biochemical products. Depending on how nutrients and substrates are supplied to the microbial culture, bioreactors are categorized as batch, continuous, or fed-batch bioreactors[5]. An effective bioreactor design enhances productivity while complying with operational standards, thereby ensuring consistent, high-quality output in a cost-efficient manner. Key design features typically include: (i) the working and headspace volumes, (ii) an integrated agitation mechanism, (iii) oxygen delivery and foam control systems, (iv) temperature and pH regulation units, (v) sampling ports, (vi) cleaning and sterilization functions, and (vii) material loading / unloading lines.

5.1. Improving penicillin production

In order to meet growing pharmaceutical demand, researchers continually seek to increase the efficiency of penicillin biosynthesis. Multiple factors influence production levels, including fermentation conditions (e.g., temperature, pH), the fungal strain employed, and the reactor configuration. Among various reactor designs, the continuous stirred tank reactor (CSTR) is considered optimal in over 70% of bioprocess applications. Its widespread adoption stems from its capacity to finely regulate reaction parameters (including temperature, pH, agitation intensity, and aeration rate) and thereby enhance penicillin yields by improving the mass transfer coefficient[6]. The latter quantifies the movement of solutes from regions of higher concentration to those of lower concentration[7]. In penicillin fermentation,

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the effective delivery of oxygen and nutrients is critical. As oxygen diffuses slowly in aqueous media, it is typically introduced in the form of air bubbles *via* filtered inlets or vacuum systems. These bubbles are then dispersed throughout the reactor through agitation, which plays a crucial role in increasing the surface area available for oxygen transfer from the gas phase to the liquid medium.

This process is governed by the volumetric mass transfer coefficient (K_La), which reflects the rate at which oxygen transitions between phases. Enhanced aeration and agitation lead to higher K_La values, and thus to improved oxygen availability, thereby resulting in increased penicillin concentrations being produced.

5.2. Methods of calculating the volumetric mass transfer coefficient

One of the earliest methods used in order to estimate K_La is sulphite oxidation[8]. In this technique, a sodium sulphite solution is stirred at controlled speeds and exposed to variable air flow rates. At regular intervals, samples are collected and titrated with sodium thiosulphate in order to measure the sulphite concentration. Plotting these values over time yields a linear graph, whose slope corresponds to the oxygen transfer rate.

The static gassing-out method[9] offers an alternative approach. Initially, oxygen is purged from the medium, commonly by introducing nitrogen. Once the dissolved oxygen level approaches zero, nitrogen flow is halted, and ambient air is introduced at a constant rate. The increase in dissolved oxygen concentration (C_L) over time can be described by the equation: $dC_L/dt=K_La(C^*-C_L)$.

A similar principle underlies the dynamic gassing-out method[10]. In the latter method, aeration is temporarily discontinued until the dissolved oxygen falls below a threshold. Once aeration resumes, real-time data on dissolved oxygen levels are collected. The rate of gas–liquid oxygen transfer is modelled using the logarithmic form: $ln((C^*-C)/(C^*-C_0))=K_La\cdot t$, where the slope of the linear relationship corresponds to $-K_La$.

6. Conclusion

Optimizing mass transfer efficiency between *Penicillium chrysogenum* and the liquid medium is central to improving penicillin synthesis in CSTR systems. This requires stringent control of operational variables (particularly mixing and aeration) so as to maintain ideal fermentation conditions.

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Conflicts of interest

None exist.

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