Journal of Biotechnology, 13 (1990) 251–256
Elsevier

BIOTEC 00435

Comparison of the performances of stirred tank and airlift tower loop reactors

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(Accepted 10 July 1989)

Summary

Following a consideration of the prerequisites for reactor comparison and the fundamental differences between stirred tank and airlift tower loop reactors, their performances are compared for the production of secondary metabolites: penicillin V by *Penicillium chrysogenum*, cephalosporin C by *Cephalosporium acremonium*, and tetracycline by *Streptomyces aureofaciens*.

In stirred tank reactors, cell mass concentrations, volumetric productivities, and specific power inputs are higher than in airlift tower loop reactors. In the latter, efficiencies of oxygen transfer are higher, and specific productivities with regard to power input, substrate and oxygen consumptions, and yield coefficients of product formation with regard to substrate and oxygen consumptions are considerably higher than in stirred tank reactors. The prerequisites for improved performance are discussed.

Stirred tank; Airlift tower loop; Penicillin; Cephalosporin; Tetracycline; Reactor performance

Introduction

Companies which manufacture products with biotechnological processes are interested in using technically and economically optimal reactors. Therefore, they

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Presented at the 2nd International Symposium on Overproduction of Microbial Products, held in České Budějovice, Czechoslovakia, 3–9 July 1988.

are looking for quality criteria to compare the performance of different reactor types. Such a comparison can be carried out on different levels: (a) based on physical properties (oxygen transfer rate (OTR), volumetric mass transfer coefficient ($k_L a$), and efficiency of oxygen transfer (E_{O_2}), mixing intensity, etc.); (b) based on cell mass productivity (Pr_X) and its efficiency (E_X) (with regard to the specific power input (P/V), as well as on substrate consumption); (c) based on the productivity (Pr_P) of primary and secondary metabolites, or of enzymes, and the efficiency of the product formation (E_P) with regard to the specific power input and substrate consumption.

The comparison based on physical properties (OTR, $k_L a$ and E_{O_2}) is the simplest one. However, several prerequisites are necessary for this comparison: (a) identical medium; (b) identical specific power input; (c) identical composition of the gas phase.

For the comparison based on the cell mass productivity and its efficiency, the following conditions are necessary: (a) identical microorganism; (b) identical substrate; (c) identical specific power input; (d) identical composition of the gas phase.

Essentially the same conditions are necessary for comparisons based on the primary metabolite and enzyme productions if the product formation is growth-coupled.

The comparisons of reactors based on the productivity of secondary metabolite productions are complicated by the following phenomena: (a) cell growth and product formation generally occur consecutively; (b) the optimal conditions for cell growth and product formation are generally different; (c) the optimal medium composition depends on the reactor type; (d) the production strain consists of different phenotypes with different properties. The selection pressure which prevails in a particular reactor yields a definite composition of subpopulations. (e) The properties of the production strain attained by mutation are adapted to a definite reactor type.

The last three of these problems also hold true for cell mass, primary metabolite, and enzyme productions, but to a lesser degree than for the production of secondary metabolites.

In the following discussion, the fundamental differences between stirred tank and tower loop reactors are first pointed out, and then the problems with reactor comparison are demonstrated using the production of three secondary metabolites: penicillin, cephalosporin and streptomycin.

Fundamental differences between stirred tank and airlift tower loop reactors

In small laboratory stirred tank reactors, the concentration and temperature distributions are nearly uniform, while these distributions are rather nonuniform in tower loop reactors due to the low intensity of the mixing of the medium. With increasing reactor size, the concentration distribution in stirred tanks (and any other reactor) becomes more and more nonuniform.

In bubble column and airlift tower loop reactors, the distribution of the energy

dissipation rate is fairly uniform in contrast to stirred tank reactors, in which the energy dissipation rate varies from the impeller edge to the reactor wall by a factor of about a hundred. A uniform energy dissipation rate is important for shear-sensitive (e.g., animal) cells, and when a definite mold morphology is desired.

Production of penicillin V by *Penicillium chrysogenum* in stirred tank and airlift tower loop reactors

Penicillium chrysogenum is similar to several other molds, in that it is able to form highly viscous filamentous mycelia as well as pellet suspensions of low viscosity. When using filamentous mycelia, a high specific power input (4–5 kW m^{-3}) is necessary to reduce the effective viscosity of the pseudoplastic medium and to supply the cells with a sufficient amount of oxygen.

When pellets are formed, the viscosity can be reduced by a factor of 4–5. The optimal medium composition and operating conditions for pellet suspension cultivations differ considerably from those for highly viscous mycelial suspensions. In order to achieve the maximum productivity, a pellet diameter of 400 μm must be maintained. Since the pellet size cannot be reduced in airlift tower loop reactors, the inoculum must contain cells which are able to form pellets with the optimal size and density after the growth phase. When using a certain strain, the suitable inoculum with small cell flocs can be prepared in a 0.02 m^3 stirred tank at 450 rpm. After inoculation, the cells gradually form the optimal-sized pellets in the airlift tower loop reactor, if the medium has the suitable composition. The optimal medium in the tower loop reactor corresponds to about the 2 : 1 diluted optimal medium of the stirred tank reactor. Furthermore, during the growth phase and at the beginning of the production phase, nitrogen limitation is maintained in order to stabilize the pellets. Since the productivities are higher with carbon limitation than with nitrogen limitation, the change from nitrogen limitation to carbon limitation should be done as early as possible. Within 20 h of this change, the pellets are dissolved. If the change occurs too early, a highly viscous liquid is formed and the cells die because of the lack of oxygen. If the change occurs at the right time, the viscosity changes only slightly, because the length and the branching of the hyphae decrease with increasing age. The oxygen supply to the cells is then sufficient.

With an optimal pellet size and operating conditions, the airlift tower loop reactors are more suitable for penicillin production than stirred tank reactors, since the latter cannot maintain the optimal pellet size (with the investigated strain) due to the strong variation of the energy dissipation rate. (It is possible that this problem does not arise with other strains, which have been mutated for pellet formation in stirred tank reactors.) A comparison of the penicillin V production in optimized stirred tank and airlift tower loop reactors with the investigated strain is shown in Table 1.

Since the raw material and/or energy costs make up 50–60% and/or 10–20% of the product formation costs, respectively, the specific productivity is the objective function of the optimization of the production and not the volumetric productivity,

TABLE 1

COMPARISON OF STIRRED TANK (ST) AND AIRLIFT TOWER LOOP REACTOR (ATL) WITH REGARD TO PENICILLIN V PRODUCTION

Specific parameters with regard to those of stirred tank	ST	ATL
Power input, P/V_L (kW m^{-3})	4–5	<1
Penicillin productivity with regard to substrate consumption (S) (kg kg^{-1} h^{-1})	1.0	1.3
Penicillin productivity with regard to oxygen consumption (O_2) (kg kg^{-1} h^{-1})	1.0	1.15
Penicillin productivity with regard to power input (P/V_L) (kg kW^{-1} h^{-1})	1.0	3.0
Penicillin productivity (kg m^{-3} h^{-1})	1.0	0.7

which influences only the fixed costs and that of the downstream processing (30% of the overall costs). Without the adaptation of cell morphology to the reactor, it is not possible to produce penicillin in airlift tower loop reactors. A comparison of these two reactor types would lead, in this case, to a preference for the stirred tank reactor.

Production of cephalosporin C by *Cephalosporium acremonium* in stirred tank and airlift tower loop reactors

The culture medium of *Cephalosporium acremonium* contains a large amount of peanut flour. The process liquid is highly viscous due to the mold cell mass and the peanut flour. Since not enough oxygen can be supplied to the mold when using such a highly viscous liquid in airlift tower loop reactors, the productivities therein are very low. A reduction in the amount of peanut flour has been found to allow a sufficient supply of oxygen to the mold in these reactors. The production was optimized in stirred tank as well as in airlift tower loop reactors. Table 2 compares the formation of cephalosporin C in these two reactor types.

The volumetric productivities are higher in stirred tanks than in the tower loop reactor, but the specific productivities and the yield coefficients are higher in the airlift tower loop reactor. This process has been developed in the industry for stirred tank reactors. Without adaptation to the airlift tower loop reactor, a comparison would have given superiority to the stirred tank reactor.

The cost structure of the production again indicates that the specific productivities are more important than the volumetric productivities because of the high fraction of the variable costs.

TABLE 2

COMPARISON OF STIRRED TANK (ST) AND AIRLIFT TOWER LOOP (ATL) REACTORS WITH REGARD TO CEPHALOSPORIN C PRODUCTION WITH DIFFERENT AMOUNTS OF PEANUT FLOUR

	Peanut flour amount (kg m^{-3})			
	30		100	
Reactor type:	ATL	ST	ST	ST
Reactor volume (m^3)	0.06	0.02	2.0	0.02
Production time (h)	150	150	130	150
Product conc. (kg m^{-3})	4.4–5.5	5.5–6.0	6.5–7.0	10–11
Productivity (g m^{-3} h^{-1})	31–34	35–38	50–54	67–73
Product yield with regard to substrate glucose, $Y_{P/S}$	0.026	0.012	0.013	0.018
Product yield with regard to methionine, $Y_{P/Met}$	0.39	0.23	0.16	0.37
Power input, P/V_L (kW m^{-3})	1.0	3.0	3.0	5.0
Oxygen transfer rate, Q_{O_2} (kg m^{-3} h^{-1})	0.64	1.2	?	2.2
Efficiency of oxygen transfer, E_{O_2} (kg kW^{-1} h^{-1})	0.64	0.4	?	0.4

TABLE 3

COMPARISON OF TETRACYCLINE PRODUCTION IN STIRRED TANK (ST) AND AIRLIFT TOWER LOOP (ATL) REACTORS

	Reactor		
	ST	ATL	ATL
Basic medium (% of the medium in ST)	100	25	50
Inoculum amount (% of the liquid volume)	5	0.5	0.5
Sucrose (kg m^{-3})	50	19	34
	(100%)	(38%)	(68%)
Lard oil (kg m^{-3})	25	1.2	0.0
	(100%)	(5%)	(0%)
Cell concentr. (kg m^{-3})	22	9.5	11
	(100%)	(43%)	(50%)
Tetracycline (kg m^{-3})	3.2	2.8	3.3
	(100%)	(88%)	(103%)
Chlortetracycline (kg m^{-3})	0.14	0.03	< 0.02
	(100%)	(21%)	(< 14%)
Productivity of tetracycline (g m^{-3} h^{-1})	32	20	27
	(100%)	(63%)	(84%)
Yield, $Y_{P/X}$ (kg kg^{-1})	0.145	0.295	0.300
	(100%)	(203%)	(207%)
Yield, $Y_{P/S}$ * (kg kg^{-1})	0.032	0.13	0.097
	(100%)	(406%)	(303%)

For $Y_{P/S}$ * it was assumed that the lard oil to sucrose energy equivalence is 2:1.

Production of tetracycline by *Streptomyces aureofaciens* in stirred tank and airlift tower loop reactors

A similar comparison of tetracycline production in these two reactors was also performed. In the stirred tank reactor, it was not possible to form and maintain pellets with the investigated strain, in contrast to the airlift tower reactor, in which small (200 μm dia.) pellets were formed. A comparison of the performances of the stirred tank reactor with filamentous mycelia and the airlift tower loop reactor with pellets is given in Table 3.

In Table 3, the medium for the production in a stirred tank was denoted as 100%. This medium was diluted 1 : 2 and 1 : 4 for use in the airlift tower loop reactor. Furthermore, only 1/10 of the inoculum amount was used in the latter.

This example supports the observation that higher specific productivities and yield coefficients can be attained in airlift tower loop reactors with pellet suspensions than in stirred tank reactors with mycelial suspensions.

Conclusion

A production process developed for a certain reactor cannot be transferred to another reactor type directly. It is necessary to reoptimize the process for the new reactor. The three examples considered here indicate that the optimal medium composition strongly depends on the reactor type. Therefore, for a proper reactor comparison, the optimization of the medium composition for each of the reactor types is necessary. In the case of penicillin and tetracycline production, reductions of the inoculum amount and, for penicillin production, changes in the inoculum quality, are also necessary.

Since such optimization is connected with high expenditures, very few investigations meet this prerequisite. Therefore, realistic reactor comparison with regard to secondary metabolite production is very rare.

Acknowledgements

The investigations of antibiotics production in different reactors were carried out by B. König, R. Wittler, T. Lorenz, J. Möller, and J. Niehoff (penicillin); T. Herold, T. Bayer and W. Zhou (cephalosporin); and A. Ross (tetracycline). The investigations were supported by the Ministry of Research and Technology of the Federal Republic of Germany, Hoechst AG (penicillin), and by the Volkswagen Foundation and Ciba-Geigy AG (cephalosporin), as well as by the Gesellschaft für Biotechnologische Forschung mbH (tetracycline).

The author gratefully acknowledges the cooperation and support of all abovementioned persons and companies.