DESIGN OF A CONTINUOUS FLOW IMMOBILIZED-CELL REACTOR FOR BIOSYNTHETICAL PRODUCTION OF L-ASPARTIC ACID

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Received October 1st 1984

An experimental study was carried out aimed at establishing a data base for an optimum design of a continuous flow fixed-bed reactor for biotransformation of ammonium fumarate to L-aspartic acid catalyzed by immobilized cells of the strain *Escherichia alcalescens* dispar group. The experimental program included studies of the effect of reactor geometry, catalytic particle size, and packed bed arrangement on reactor hydrodynamics and on the rate of substrate conversion. An expression for the effective reaction rate was derived including the effect of mass transfer and conditions of the safe conversion-data scale-up were defined. Suggestions for the design of a pilot plant reactor (100 t/year) were formulated and decisive design parameters of such reactor were estimated for several variants of problem formulation.

Regarding both technological aspects and process economy, biotransformation of ammonium fumarate on immobilized bacterial cells has been proved to be the only feasible way of L-aspartic acid production applicable on an industrial scale. It was established previously that the strain *Escherichia alcalescens* dispar group[1] entrapped in polyacrylamide gel catalyzed effectively the conversion of ammonium fumarate to L-aspartic acid. Experimental data[2] proved both high transformation activity and long functional stability of the system suggesting thus its suitability for an industrial use. Regarding these conclusions, the main goal of our present study was to obtain a data base for an optimum design of a large-scale continuous flow reactor for the production of L-aspartic acid. Apparently, the continuous flow arrangement has been advantageous in this case both for process economy and technological reasons (elimination of nonproductive time periods, reduction of gel losses due to concentration stress and mechanical attrition). Packed-bed upflow reactor was chosen regarding the process demands and properties of the biocatalytic system used. In comparison with stirred suspended-cells reactor this reactor configuration eliminates mechanical cells attrition, the filtration step can be avoided and the demands on energy supply are minimized. The program of our experimental study included determination of optimum packed-bed arrangement, estimation

of the particle size effect on the overall reaction rate, and determination of the effect of reactor scale-up on substrate conversion and/or on specific reactor productivity. Transient characteristics of the system were also obtained as a base for determination of dynamic parameters of the reactor and for subsequent development of a reactor control algorithm.

EXPERIMENTAL

Equipment and experimental conditions. The experimental set-up is shown schematically in Fig. 1. Programmable controller PCS-1 developed in our institute was used for reactor control and regulation. Three cylindrical glass-wall reactors 0·026, 0·047, and 0·108 m in diameter were used for experiments, their respective heights were 0·20, 0·50, and 0·55 m. Substrate feed was distributed at the reactor bottom by sintered-glass plates (in reactors 0·026 and 0·047 m I.D.) or by a stainless steel perforated plate (holes diameter 0·001 m) covered from both sides by a stainless steel micromesh screens. The effective reactor volume was determined by the position of an adjustable piston with a central tube for reaction product withdrawal. A peristaltic pump with continuous regulation was used for substrate dosing. Product composition was determined by an UV analyzer at wavelength 254 nm. The analyzer signal was monitored by a digital voltmeter and registered on a recorder. Experiments were performed with 1M ammonium fumarate at pH = 8·5, reaction temperature was 37°C. Prior to experiments, the cells were activated for 24 hours under reaction conditions. Four charges of immobilized cells were prepared for experiments, individual fractions of crushed gel particles were separated in a flotation column[3] using partially transformed substrate as a flotation medium. Range of particle sizes within fractions and the average particle dimensions, $\bar{d}_i$, characterizing individual fractions, were determined by microscopic analysis of particles samples. Characteristics of all fractions used for experiments are given in Table I. Kieselguhr Hiflo-super cell was used as an inert phase in experiments with diuted packed beds.

Optimization of packed bed arrangement. The effect of packed bed arrangement on its permeability and on substrate conversion was studied in reactors 0·026 and 0·047 m in diameter.

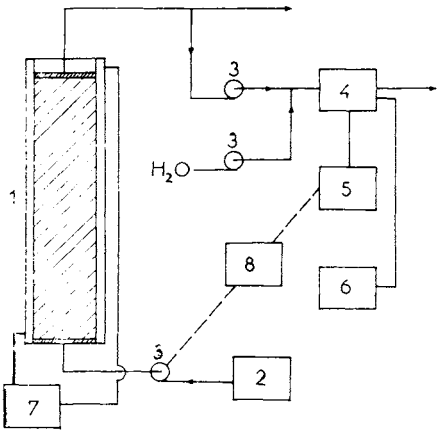

FIG. 1

Experimental set-up. *1* reactor, *2* substrate-storage vessel, *3* pumps, *4* UV analyzer, *5* digital voltmeter, *6* recorder, *7* thermostat, *8* controller

Experiments were carried out with unseparated finely grained particles of charge 1 (fraction 1N, $\bar{d}_{1N} = 0{\cdot}1$ mm), with particles of this fraction diluted by kieselguhr in ratios 1 : 1 and 1 : 2, and with four fractions of coarsely grained particles of charge 2 (2A, 2B, 2C, 2D — see Table I). Values of specific reactor productivity, Q_r, characterizing the rate of substrate transformation in a unit of packed bed volume, and of the degree of biocatalyst utilization, Φ, defined as a volume of substrate transformed in a time unit related to a unit of mass of active particles in the bed were evaluated from conversion data obtained at various substrate feed rates. It was the goal of this set of experiments to define optimum packed bed arrangement regarding its permeability (stability of substrate flow regime) and reactor productivity.

The effect of particle size on reaction rate. The effective reaction kinetics including the contribution of mass transfer to the overall reaction rate was measured in the column 0·026 m in diameter for particles fractions 3B ($d = 0{\cdot}2-0{\cdot}8$ mm), 3C ($d = 0{\cdot}8-1{\cdot}8$ mm), and 3D ($d = 1{\cdot}8$ to 5·0 mm). All experiments were performed at constant mass of particles bed, $m_r \approx 40$ g, mean packed bed density, $\varrho_c = m_c/V_c$, and consequently also the packed bed volume, V_c, were practically independent of particles size ($\varrho_c \approx 0{\cdot}62$ g/cm^3, $V_c \approx 76$ cm^3). Substrate conversion, X, was determined as a function of parameter τ corresponding to the reciprocal value of specific substrate feed rate related to a unit of packed bed volume, $\tau = V_c/\dot{V}_L$. The reaction order to substrate was evaluated from experimental kinetic data and the effect of particles size on value of effective reaction rate constant was estimated from data obtained for individual particles fractions.

Reactor scale up. The effect of packed bed geometry (H, D, H/D) on the dependence of substrate conversion on its flow rate was studied in all experimental reactors ($D = 0{\cdot}026$; 0·047;

TABLE I
Characteristics of particles fractions

Charge	Degree of grinding	Fraction number	Range of particle sizes mm	$\bar{d}_i$ mm
1	fine	1N	unseparated	0·1
2	coarse	2A	0·2—5·0	2·6
		2B	0·2—0·8	0·5
		2C	0·8—1·8	1·3
		2D	1·8—5·0	3·4
3	coarse	3A	0·2—5·0	2·6
		3B	0·2—0·8	0·5
		3C	0·8—1·8	1·3
		3D	1·8—5·0	3·4
4	coarse	4A	0·2—5·0	2·6
		4B	0·2—0·8	0·5
		4C	0·8—1·8	1·3
		4D	1·8—5·0	3·4

0·108 m) within the range of $H/D = 1-10$. Experiments were performed with particles fraction 4C ($d = 0{\cdot}8-1{\cdot}8$ mm). It was our purpose to define conditions of reliable conversion data transfer from a laboratory reactor to large-scale units.

Reactor dynamics. System transient responses to step changes of substrate feed rate were determined in all experimental reactors at various H/D ratios and substrate flow rates to obtain informations on reactor dynamics in a wide range of substrate conversions. The experiments covered conversion region 0·27—0·994, corresponding values of substrate flow rate related to free reactor cross-section ranged between 1·1 and 13·2 ml cm^{-2} h^{-1}.

RESULTS AND DISCUSSION

Optimization of Packed Bed Arrangement

Experiments performed with unseparated fine particles (fraction 1N) proved that permeability of such beds worsened substantially with increasing height of the bed and with increasing substrate flow rate limiting thus the existence of stable flow regime (and consequently region of stable reactor performance) to low bed heights ($H/D \leqq 2$) and small substrate feed rates ($\dot{V}_L/m_c \leqq 7$ ml/g h at $H/D = 1$; $\dot{V}_L/m_c \leqq$ $\leqq 5$ ml/g h at $H/D = 2$). Beyond this range significant channeling occurred, the bed was torn apart to separate horizontal layers and finally it became completely unpermeable already after less than one hour of reactor operation. The effect of bed dilution on its permeability was therefore tested under comparable conditions ($D =$ $= 0{\cdot}026$ m, fraction 1N, $H/D = 1-7{\cdot}7$) using kieselguhr as an inert material. The experimental results proved that even the dilution ratio 1 : 1 did not ensure a long-term stabilization of substrate flow in the whole range of feed rates and bed heights. Further increase of dilution ratio caused on the other hand significant decrease of biocatalyst utilization ratio, Φ, apparently due to worsened contact between substrate and catalytically active particles in such strongly diluted beds. As a result, even larger decrease of specific reactor productivity, Q_r, was observed in such cases than would be proportional to the part of overall bed volume occupied by inert particles. As an illustration, data of substrate conversion, Q_r, and Φ obtained in the reactor 0·026 m in diameter in an undiluted bed of fine particles (fraction 1N) and in beds of such particles diluted by kieselguhr in ratios 1 : 1 and 1 : 2 are shown in Table II.

Regarding the drawbacks of packed bed dilution, application of larger particles was tested as a possible alternative way of packed bed permeability improvement. These experiments were carried out in reactors 0·206 and 0·047 m I.D. with coarsely grained particles of charge 2 including narrow fractions 2B, 2C, 2D (Table I) and the lumped fraction 2A ($d = 0{\cdot}2-5{\cdot}0$ mm). In all cases good permeability and flow regime stability was observed during long-term runs ($t \sim 10^2$ h) independently of substrate flow rates up to H/D equal 10 ($H = 0{\cdot}2$ m, $D = 0{\cdot}026$ m; $H = 0{\cdot}5$ m, $D = 0{\cdot}047$ m). No changes of flow regime and character of packed bed were observed

even after repeated shut off and subsequent start of substrate dosing. Undiluted beds of such larger particles (charges 2–4, $d = 0{\cdot}2-5{\cdot}0$ mm) were therefore used in all further experiments and are to be recommended for industrial applications.

The Effect of Particle Size on Reaction Rate

In Fig. 2 conversion data obtained for individual particle fractions were plotted in the form $\lg(1/(1-x))$ *vs* τ. Apparently, linear shape of such graphs corresponded to the reaction of the first order to ammonium fumarate and the data could be well correlated by equation

$$\lg(1/(1-x)) = k_{ef}\tau\,, \qquad (1)$$

Table II

The effect of packed bed dilution by an inert material $D = 0{\cdot}026$ m, $m_{cat} = 13{\cdot}1$ g, fraction 1N (dilution ratio = $m_{cat} : m_{inert}$)

Dilution ratio	V_c cm^3	$\dot{V}_L$ ml	X %	Q_r ml cm^{-3} h^{-1}	Φ ml g_{cat}^{-1} h^{-1}
Undiluted	21	30	97·3	1·39	2·23
bed	21	40	92·4	1·76	2·82
1 : 1	36	30	98·3	0·82	2·25
1 : 1	36	40	94·3	1·05	2·88
1 : 2	52	30	84·7	0·49	1·94
1 : 2	52	40	68·8	0·53	2·10

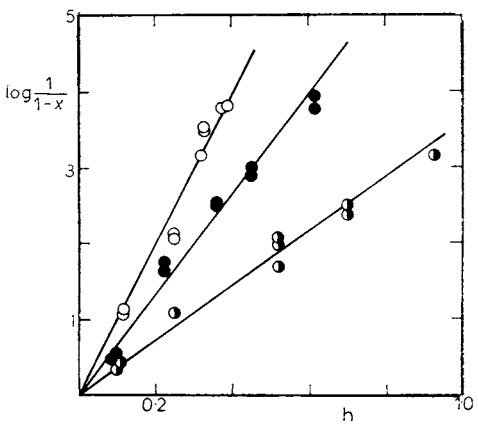

Fig. 2

Effective reaction kinetics for different fractions of particles. ○ $d = 0{\cdot}2-0{\cdot}8$ mm, ● $d = 0{\cdot}8-1{\cdot}8$ mm, ◐ $d = 1{\cdot}8-5{\cdot}0$ mm

where the effective rate constant k_{ef} included the effect of intraparticle mass transport. Values k_{ef} obtained for individual fractions as slopes of corresponding straight lines presented in Fig. 2 were then in Fig. 3 plotted against characteristic particle dimensions, $\bar{d}_i$. As can be seen from Fig. 3, the dependence k_{ef} *vs* $\bar{d}_i$ was in the experimental region of particle sizes ($d = 0{\cdot}2-5{\cdot}0$ mm) well described by an empirical exponential type relation

$$k_{ef} = a \,.\, b^{\bar{d}_i} + c \qquad (2a)$$

for values of coefficients $a = 9{\cdot}84$, $b = 0{\cdot}54$, $c = 2{\cdot}25$ obtained from the experimental data.

Reactor Scale Up

In Fig. 4 data $\lg(1/(1-x))$ *vs* τ were plotted for individual values of reactor diameter and bed height (H/D ratio). As can be seen from the figure, the dependence of substrate conversion on its flow rate observed at low bed heights ($H/D \leqq 2$) in reacs tors 0·026 and 0·047 m I.D. was much less pronounced than at high H/D ratio-

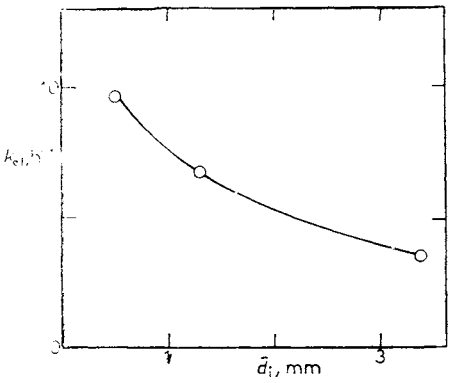

Fig. 3

Dependence of effective rate constants on the particle size

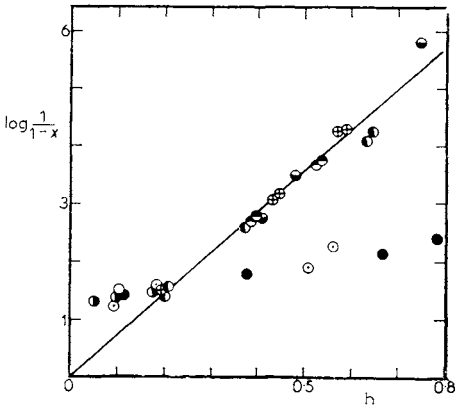

Fig. 4

The effect of packed-bed geometry on conversion data. ○ $D = 0{\cdot}026$ m, $H/D = 1$; ● $D = 0{\cdot}026$ m, $H/D = 2$; ◐ $D = 0{\cdot}026$ m, $H/D = 5$; ◑ $D = 0{\cdot}047$ m, $H/D = 1$; ⊙ $D = 0{\cdot}047$ m, $H/D = 2$; ⊕ $D = 0{\cdot}047$ m, $H/D = 5$; ◓ $D = 0{\cdot}047$ m, $H/D = 10$; ◒ $D = 0{\cdot}108$ m, $H/D = 1$. The data calculated from Eq. (*1*) for $k_{ef} = 7{\cdot}17\ h^{-1}$

($H/D \geqq 5$). Lower conversions achieved in these reactors at low H/D ratios for $\tau \geqq 0{\cdot}2$ (*i.e.* at low substrate flow rates) can be apparently ascribed to unsufficient contact of substrate with external surface of particles in the bed caused by substrate maldistribution at the reactor inlet. Whereas its negative effect has been in high beds compensated by additional substrate redistribution along the bed height, significant bypassing alongside the reactor walls and channeling were observed visually in low beds at low substrate flow rates. Quality of inlet substrate distribution improved significantly with its increasing flow rate and as a result no effect of bed height (H/D ratio) on conversion data was observed in reactors 0·026 and 0·047 m I.D. at low values of τ. Unlike in the two small diameter reactors (0·026 and 0·047 m I.D.), conversion data obtained in the reactor 0·108 m in diameter at $H/D = 1$ did not deviate from those corresponding to high H/D ratios even in the region of high values of τ ($\tau > 0{\cdot}2$). Apparently this confirmed decreasing importance of the flow alongside walls with reactor diameter increase. Comparison of the trends exhibited by conversion data (Fig. 4) with substrate flow rates related to the free reactor cross-section, $w_L = \dot{V}_L/A$, which are presented for typical experimental runs in Table III, proved that the values of substrate flow rates corresponding to the onset of uniform particles wetting decreased with increasing bed height and with increasing reactor diameter. Apparently this further confirms our qualitative assumptions concerning the additional substrate redistribution along the bed height and decreasing importance of the "wall-flow" contribution with increasing reactor diameter. It can be generally postulated that to ensure reliable transition of laboratory kinetic data to an industrial scale, the laboratory experiments have to be performed under conditions of uniform particles wetting, *i.e.* under conditions when the substrate conversion depends on parameter τ only, independently of bed geometry. It has been apparent from data presented in Fig. 4 and in Table III that in our case (*i.e.* for the process studied and for selected type of substrate distributor) such conditions were achieved in the whole range of D and H/D values at substrate flow rates $w_L \geqq 6 \cdot 10^{-5}$ m s^{-1}. The results of our scale up study further suggest that the reactor scale up has favourable effect on the stability and uniformity of substrate flow through the bed, *i.e.* on the uniformity of particles wetting. The conversion data obtained in our laboratory reactor 0·108 m in diameter can be thus apparently recommended for large-scale reactor calculation assuming constant efficiency of inlet substrate distribution and sufficient rate of substrate feed fulfilling the condition $w_L \geqq 6 \cdot 10^{-5}$ m s^{-1}.

Conversion data obtained in all reactors under conditions of uniform bed wetting ($x \neq f(D, H/D)$) were correlated by Eq. (*1*). The least squares method yielded value of effective rate constant $k_{ef} = 7{\cdot}2$ g^{-1}. As can be seen from Fig. 4 good agreement was observed between experimental data and values calculated from Eq. (*1*) for this k_{ef} value. As was reported above, value $k_{ef} = 6{\cdot}7$ h^{-1} was determined during our studies of particle size effect for fraction 3C having the same region of particle sizes ($d = 0{\cdot}8 - 1{\cdot}8$ mm) as fraction 4C used in scale up experiments. The agreement of the

two k_{ef} values can be considered as a fairly satisfying regarding the fact that the methods of particles separation and grain size analysis did not ensure identical particle size distribution within fractions with constant particle size limits. The agreement of k_{ef} values for fractions 3C and 4C thus proved good reproducibility of the procedure used for preparation of catalytically active particles and of the particles separation method. The empirical relation

$$k_{ef} = 9{\cdot}84 \,.\, 0{\cdot}54^{d_1} + 2{\cdot}25 \qquad (2b)$$

can be therefore used with sufficient accuracy for prediction of an effective rate con-

TABLE III
Conditions of scale up experiments

D m	H/D —	m_c g	$\dot{V}_L$ ml h^{-1}	τ h	x —	$\dot{V}_L/m_c$ ml g^{-1} h^{-1}	$w_L \,.\, 10^{-5}$ m s^{-1}
0·026	1	8·5	131	0·105	0·772	15·3	6·9
0·026	1	8·5	286	0·048	0·610	33·4	15·2
0·026	2	17	36	0·758	0·911	2·1	1·9
0·026	2	17	41	0·682	0·892	2·4	2·2
0·026	2	17	73	0·378	0·838	4·3	3·8
0·026	2	17	254	0·109	0·770	14·9	13·3
0·026	2	17	283	0·097	0·763	16·6	14·8
0·026	5	43	107	0·644	0·986	2·5	5·6
0·026	5	43	184	0·375	0·925	4·3	9·6
0·026	5	43	331	0·208	0·817	7·7	17·3
0·047	1	54	492	0·176	0·769	9·2	7·9
0·047	1	54	857	0·101	0·757	15·9	13·7
0·047	1	54	1 737	0·050	0·751	32·3	27·8
0·047	2	108	310	0·560	0·893	2·9	5·0
0·047	2	108	340	0·511	0·898	3·2	5·4
0·047	2	108	968	0·179	0·797	9·0	15·5
0·047	2	108	1 931	0·090	0·775	17·9	30·9
0·047	5	269	763	0·569	0·986	2·8	12·2
0·047	5	269	970	0·447	0·957	3·6	15·5
0·047	5	269	2 323	0·187	0·791	8·7	37·2
0·047	10	537	1 603	0·541	0·977	3·0	35·7
0·047	10	537	2 200	0·395	0·939	4·1	35·2
0·108	1	613	1 320	0·749	0·998	2·1	4·0
0·108	1	613	1 560	0·634	0·997	2·5	4·7
0·108	1	613	2 045	0·484	0·970	3·4	6·2
0·108	1	613	2 450	0·404	0·925	4·0	7·4

stant within the whole experimental range of particle sizes, $d = 0{\cdot}2 - 5$ mm. In Eq. (*1*), parameter τ can be expressed from its definition as $\tau = m_c/\varrho_c \dot{V}_L$ and after substitution for k_{ef} from Eq. (*2b*) and further rearrangement, Eq. (*3*) can be obtained for reactor calculation in the form

$$m_c/\varrho_c \dot{V}_L = \lg\left(1/(1 - x)\right)/(9{\cdot}84 \,.\, 0{\cdot}54^{\bar{d}_1} + 2{\cdot}25) \,. \qquad (3)$$

It is obvious that the value of substrate flow rate, $\dot{V}_L$, is determined by the required capacity. The corresponding catalyst mass in the bed can be then directly estimated from Eq. (*3*) for a specified particles fraction and required substrate conversion.

Reactor Dynamics

System transient characteristics were determined in individual reactors within different regions of substrate conversions. As an illustration, transient response curves are presented in Fig. 5 obtained in the reactor 0·108 m in diameter at $H/D = 1$ with particles of standard activity (fraction 4C) within the expected range of reactor operation conditions, *i.e.* between substrate conversions $x = 0{\cdot}875$ to 0·995. The dynamic parameters of the reactor were determined from the response curves and an appropriate control algorithm was developed and introduced into the memory of the programmable controller PCS-1. This algorithm was then tested with satisfactory results both in a simulation regime and experimentally under conditions of real reactor performance[4]. Detailed treatment of the reactor control and regulation problems lies however beyond the scope of the present paper and will be published later separately.

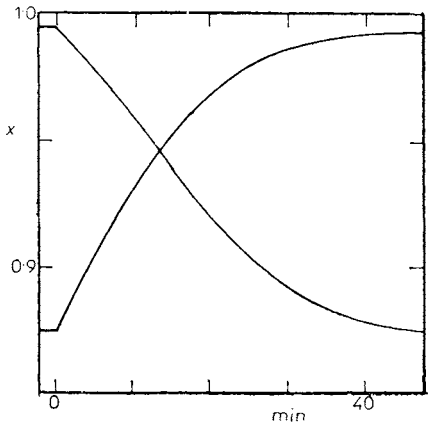

Fig. 5

Examples of transient curves $D = 0{\cdot}108$ m, $H/D = 1$, fraction 4C ($d = 0{\cdot}8 - 1{\cdot}8$ mm)

Pilot-Plant Reactor Design

Decisive design parameters of a pilot-plant reactor with production capacity 100 t of L-aspartic acid per year were calculated to illustrate the effect of process and operation parameters on the reactor size and to establish a basis for final specification of demands on industrial reactor design. The adjustable input parameters representing initial conditions for reactor calculation included overall time of reactor performance per year, required substrate conversion, and particle size. Selected values of these parameters are summarized in Table IV. Altogether forty reactor variants were calculated corresponding to appropriate combinations of individual input parameters. Standard activity of the biocatalytic system was assumed corresponding to conditions of our laboratory experiments and constant value of packed-bed density, $\varrho_c = 0{\cdot}62\ \mathrm{g\,cm^{-3}}$, was used in calculations. Values of rate constants, $k_{ef} = 7{\cdot}17\ \mathrm{h^{-1}}$ and $4{\cdot}23\ \mathrm{h^{-1}}$ were determined for characteristic dimensions of selected particle fractions, $\bar{d}_i = 1{\cdot}3$ and 2·6 mm from Eq. (*2b*).

As the first step of calculation, values of substrate flow rate, $\dot{V}_L$, corresponding to required reactor capacity were determined for individual values of operation time, t_{op}. The overall packed bed volume and the mass of particles in the bed were then calculated from Eq. (*4*) for specific values of effective rate constants and substrate conversion

$$V_c = m_c/\varrho_c = \dot{V}_L \lg\left(1/(1 - x)\right)/k_{ef} \,. \qquad (4)$$

Table IV

Mass of catalyst particles calculated for individual variants of the pilot-plant reactor

Conversion %	d_i mm	Operation time h/year			
		8 760	6 240	2 920	2 080
99·0	1·3	34·2	47·9	102·4	143·8
99·0	2·6	57·9	81·3	173·7	243·9
99·9	1·3	51·2	71·9	153·6	215·7
99·9	2·6	86·9	121·9	260·5	365·7
99·99	1·3	68·3	95·9	204·8	287·5
99·99	2·6	115·8	162·5	347·3	487·6
99·999	1·3	85·4	119·8	256·1	359·4
99·999	2·6	144·8	203·2	434·2	609·6
99·9999	1·3	102·4	143·8	307·3	431·3
99·9999	2·6	173·7	243·8	521·0	731·4

Calculated values of catalyst particles mass, m_c, are presented in Table IV. As can be seen from the table, m_c values varied between 34·2 kg for t_{op} = 8 760 h/year, X = = 99·0%, and k_{ef} = 7·17 h^{-1} and 731·4 kg for t_{op} = 2 080 h/year, X = 99·9999%, and k_{ef} = 4·23 h^{-1}, corresponding values of packed bed volume were 0·055 and 1·18 m^3. Limiting (maximum allowed) values of reactor diameter, D_{max}, corresponding to specific substrate feed rates (*i.e.* to individual values of t_{op}) were determined from the condition of uniform particles wetting, $\dot{V}_L/A \geqq w_{Lmin} = 6 . 10^{-5}$ m/s,

$$D_{max} = 2(\dot{V}_L/\pi w_{Lmin})^{1/2} \tag{5}$$

and appropriate values of minimum bed height $H_{min} = 4 . V_c/\pi D^2_{max}$ and H/D ratio, $(H/D)_{min} = H_{min}/D_{max}$, were calculated for individual values of packed bed volume. The calculation yielded values of D_{max} ranging between 0·71 m (for $\dot{V}_L$ = = 0·086 m^3/h, t_{op} = 8 760 h/year) and 1·46 m (for $\dot{V}_L$ = 0·361 m^3/h, t_{op} = 2 080 h/year), corresponding values of H_{min} and $(H/D)_{min}$ varied in dependence on k_{ef} and x in regions H_{min} = 0·14–0·71 m, $(H/D)_{min}$ = 0·2–1·0.

It can be however envisioned that regarding the construction and technological reasons significantly lower values of reactor diameter are likely to be chosen for a pilot-plant reactor in comparison with respective maximum allowed values D_{max}. Correspondingly then, the appropriate values of bed height will be higher than the values H_{min}. In such cases however tolerable limits of bed height increase have to be estimated cautiously regarding the consequent increase of pressure drop and its possible negative effect on stability of substrate flow and packed-bed permeability. Considering the results of our study it can be assumed that the reactor scale up should not cause significant problems within the regions $H/D \leqq 5$ and $H \leqq 1·5$ m. Further increase of bed height (H/D ratio) should not be however designed without preliminary tests of reactor hydrodynamics (character of substrate flow) carried out preferably on a pilot-plant scale. Sectionalization of the bed by horizontal perforated plates into separate stages fulfilling the conditions $H_i/D \leqq 5$, $H_i \approx 0·5 - 1$ m, can be recommended as an alternative solution in such cases. Installation of such plates would indeed cause the increase of reactor pressure drop, on the other hand however the plates, beside their supporting function, ensure substrate redistribution and thus reduce possible negative effects of channeling and of the bypass-flow along the walls.

As it was stated above the reactor control and regulation has been based upon the analysis of reaction product at the reactor outlet. Regarding high demands on product purity (substrate conversion) and consequently on the accuracy of measurement in the vicinity of total substrate conversion it may be advisable to substitute a single stage reactor by a cascade of two vessels with identical volume of individual stages ($V_1 = V_2 = V/2$). In such an arrangement it would be sufficient to analyse the outlet stream from the first stage which would lower the demands on accuracy

of analysis, *e.g.* from 99·9 to 90·0% or from 99·9999 to 99·9%. The two-stage reactor arrangement would be apparently advantageous even from the viewpoint of cells viability and constant activity. A periodic reversal of stages sequence in the cascade would prevent all cells from undesirable long-term contact with almost fully transformed substrate which cannot be avoided in upper layers of packed beds in single-vessel reactors.

LIST OF SYMBOLS

a, b, c coefficients in Eq. (2)
A reactor cross-section
d particle diameter
$\bar{d}_i$ characteristic dimension of particles in individual fractions
D reactor diameter
H height of packed bed
m_c mass of particles in the bed
Q_r specific reactor productivity
t time
V_c volume of packed bed
$\dot{V}_L$ substrate flow rate
w_L substrate flow rate related to a unit of reactor cross-section ($w_L = \dot{V}_L/A$)
x substrate conversion
X substrate conversion in percents
ϱ_c average density of packed bed
τ characteristic parameter defined as a ratio of packed bed volume to the rate of substrate flow ($\tau = V_c/\dot{V}_L$)
Φ degree of biocatalyst utilization

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