Process Intensification of Nicotinic Acid Production via Enzymatic Conversion using Reactive Extraction

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Nicotinic acid is widely used in the food, pharmaceutical and biochemical industries. Compared to chemical methods, enzymatic conversion of 3-cyanopyridine is an advantageous alternative for the production of nicotinic acid and nicotinamide. The separation of the product is complicated, owing to its high dilution rate in fermentation broth and high cost. Reactive liquid-liquid extraction by a suitable extractant system has been found to be a promising alternative to the other conventional separation techniques. This paper gives a state-of-the-art review for manufacturing processes (chemical and enzymatic) of nicotinic acid and nicotinamide. It also focuses on the most efficient separation technique, reactive extraction. Reactive extraction has advantages of less consumption of material and energy. It also avoids product inhibition and increases the separation selectivity.

Key words:
Nicotinic acid, enzymatic conversion, process intensification, separation, reactive extraction

Introduction

Niacin, also known as nicotinic acid or vitamin B3, is a water-soluble vitamin whose derivatives such as NADH (reduced form of NAD, nicotinamide-adenine-dinucleotide) play essential roles in energy metabolism in the living cell. The designation vitamin B3 also includes the amide form, nicotinamide or niacinamide. Both compounds participate in the formation of NAD and NADP (nicotinamide-adenine-dinucleotide-phosphate) coenzymes, playing a key-role in the redox reactions in cells.[1–6] Its usage as a bio stimulator for the formation of activated sludge and as a deodorant of air and waste gases in pollution control is important. Nicotinamide is the form of niacin typically used in nutritional supplements and in food fortification.[7]

Nicotinic acid is required as an essential component of foodstuff for balanced diet requirements. Good sources of niacin are yeast, meat, poultry, red fish (e.g. tuna, salmon), cereals (especially fortified cereals), legumes, and seeds. Milk, green leafy vegetables, coffee, and tea also provide some niacin.[8] Niacin, when taken in large doses, blocks the breakdown of fats in adipose tissue, thus altering blood lipid levels. Hence, niacin is useful in the treatment of hyperlipidemia.[9,10] The use of niacin in sports is illegal if it is consumed in large quantities to fool drug screening tests, particularly for lipid-soluble drugs such as marijuana.[11]

The recommended daily allowance range of niacin is 2–12 mg for children, 14 mg for women, 16 mg for men, and 18 mg for expectant or nursing mothers.[12] A deficiency of nicotinic acid causes pellagra, a serious disease that has plagued mankind for centuries, while a mild deficiency slows down the metabolism, causing decreased tolerance to cold. Dietary niacin deficiency tends to occur only in the areas where people eat corn (maize) – the only grain low in niacin – as a staple food, and that do not use lime during meal/flour production.[13] Alkali lime releases the tryptophan from the corn which is converted to niacin.[8] The most common symptoms of niacin deficiency involve the skin, digestive system, and the nervous system. Other symptoms of pellagra are dermatitis, red tongue, vomiting, diarrhea, headache, apathy, depression, disorientation, and memory loss.[4,13] Its prevention and treatment include niacin in the dietary intake, in relation with age, sex, and the health of the subjects. It was also observed that niacin plays an important role in the causes and treatments of other diseases, such as cancer,[14–18] diabetes[19–21] and cardiovascular diseases associated with high level of cholesterol[10,22–24] and AIDS.[25,26] Since, the human body does not have the ability to produce niacin, its intake by food and/or nutritional supplements rep-

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resents the main way for avoiding niacin deficiency. As niacin is important for human life, its worldwide production has strongly increased in the last several years to about 22,000 tons/year (over 65 % is nicotinic acid). The major producers of nicotinic acid are Lonza (Switzerland), Degussa, BASF (Germany), Nepera, Reilly Industries (ex-Vitachem) (US), and Yuki Gosei (Japan).[27,28]

This paper gives a state-of-the-art review for manufacturing processes (chemical and enzymatic) of nicotinic acid and nicotinamide. It also covers recent separation technique, reactive extraction with a specified extractant system. This method is proposed as a promising technique for nicotinic acid separation in terms of intensifying nicotinic acid production.

Nicotinic acid production

3-Picoline is used as an ideal starting material for the production of nicotinic acid or amide. In 3-picoline, the methyl group can be selectively and readily oxidized to the carboxyl derivative with few side-products or pollutants. 2-Methyl-5-ethyl-pyridine (MEP) is also used as a starting material for the high temperature and pressure liquid-phase oxidation with nitric acid, but it is not a good choice.[29] The disadvantage of the process is the handling of nitric acid at elevated temperatures and pressure. From the ecological standpoint, the intrinsic loss of two carbon atoms in the form of carbon dioxide makes the use of MEP unattractive. High selectivity and low amount ratio ($r = 1 : 1.3$) compared to the end-products make 3-picoline an attractive industrial starting material. 3-Picoline typically, in the ratio of $r = 1 : 2$ along with the main product pyridine is synthesized by the gas-phase reaction of acetaldehyde, formaldehyde and ammonia.[30] 3-Picoline is first converted to 3-cyanopyridine by gas-phase ammoxidation followed by hydrolysis either to nicotinamide or nicotinic acid as shown in Fig. 1. These commercial processes, for the production of nicotinic acid and nicotinamide, represent the most logical and direct route via 3-picoline. The production of nicotinamide or nicotinic acid through ammoxidation reaction has received greater attention in the past 15 years, both in industry[31–33] and in academic institutions.[34–37]

For over 60 years, direct gas-phase oxidation of 3-picoline using vanadium oxide catalysts has also been known to produce nicotinic acid.[38,39] The reaction scheme for this direct gas-phase oxidation of 3-picoline is given in Fig. 2. This process has

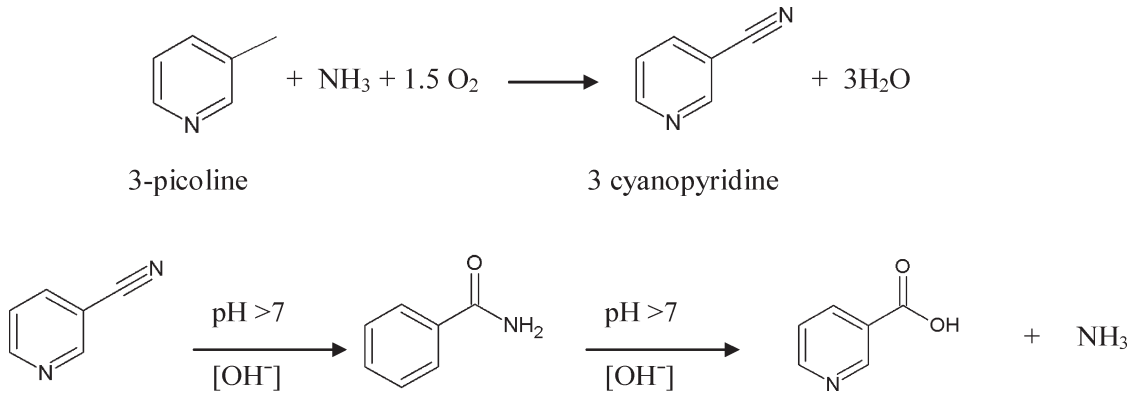


Fig. 1 – *Gas-phase ammoxidation of 3-picoline followed by hydrolysis of cyanopyridine to nicotinamide and nicotinic acid*

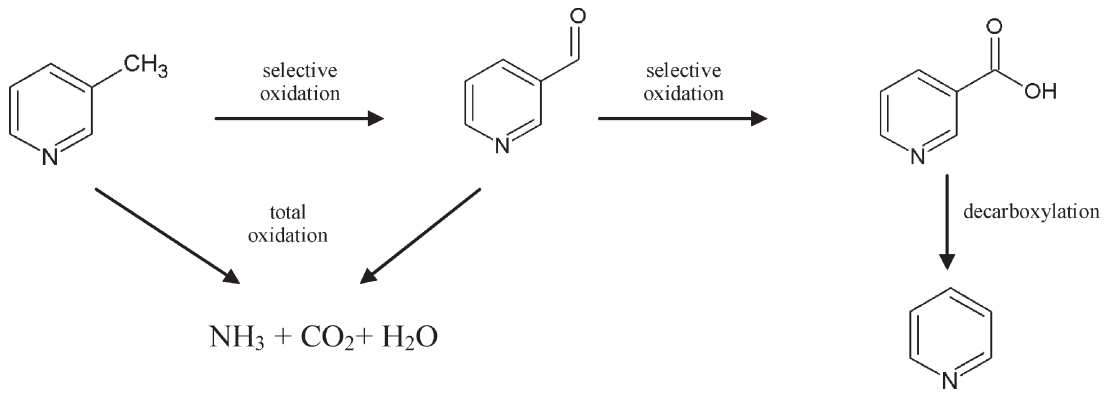


Fig. 2 – *Reactions involved in direct gas-phase oxidation of 3-picoline to nicotinic acid*

considerable difficulties in obtaining a selective and efficient reaction in gas-phase. Also, nicotinic acid is less stable than 3-cyanopyridine and decarboxylates at the temperatures normally encountered in the gas-phase reaction. In addition, nicotinic acid desublimes at temperatures below 200 °C and thus can create plugging difficulties in the equipment.

Picoline can also be selectively oxidized with air in the liquid phase to produce niacin.[40] A catalyst combination such as cobalt and manganese acetate and/or bromide is usually used in an acetic acid medium. This air-oxidation takes place at elevated temperature and pressure. The disadvantages of this process are that additional cleaning and processing steps are required to ensure the desired purity and physical properties of the product. The mother-liquor contains metallic catalysts which must be recycled if the process is to be efficient. Some companies[41–44] in Japan have employed liquid-phase oxidation of 3-picoline to niacin on a commercial scale.

3-Cyanopyridine first has to be selectively hydrolyzed to prepare niacin and niacinamide. The hydrolysis is usually carried out in the presence of a strongly basic catalyst that generates some nicotinate salt. This has to be removed to obtain pure niacinamide and niacin. Both Reilly[45,46] and Degussa[47,48] describe processes involving strong bases and subsequent purification using ion-exchangers. One main drawback of the chemical hydrolysis is that inevitably some nicotinate salt is produced due to over-hydrolysis of cyanopyridine.

Enzymatic conversion

The process to produce nicotinic acid and nicotinamide can be intensified by enzymatic conversion of 3-cyanopyridine or biosynthesis. In recent years, the application of enzymes to organic chemical processing has attracted increasing attention. Enzymes are operated under mild conditions suitable for the synthesis of labile organic molecules and are efficient in terms of specificity. Nitrilases enzymes are gaining popularity as biocatalysts for the mild and selective hydrolysis of nitriles. Nitrilases with diverse substrate specificities are purified from bacteria.[49] Asano *et al.*[50] proposed an enzymatic production process for acrylamide involving nitrile hydratase as a catalyst. Mathew *et al.*[51] attempted the microbial conversion of 3-cyanopyridine to nicotinic acid by using resting *R. rhodochrous* JI cells containing high benzonitrilase activity. This process is promising for industrial production of nicotinic acid with features of total conversion (100 %) of 3-cyanopyridine under mild conditions and easy cultivation of *R. rhodochrous* Jl cells. Peter *et al.*[52] converted 3-cyanopyridine to nicotinic acid by *Nocardia rhodochrous* LL100-21. The bacteria is immobilized in calcium alginate beads and used in column bioreactors retained 3-cyanopyridinase activity for over 150 h when continuously supplied with 0.3 mol L^{-1} of 3-cyanopyridine. A thermostable nitrilase produced by the thermophilic bacterium *Bacillus pallidus* Dac521 catalyzed the direct hydrolysis of 3-cyanopyridine to nicotinic acid without detectable formation of nicotinamide.[53] Under optimized conditions, 100 % of the 3-cyanopyridine substrate could be converted to nicotinic acid at a conversion rate of 76 nmol min^{-1} mg^{-1} dry cell mass.[53] Kaplan *et al.*[54] also performed biotransformation of 3-cyanopyridine into nicotinic acid by fungal nitrilases. Very recently, Maria *et al.*[55] performed amidase-catalyzed production of nicotinic acid in batch and continuous stirred membrane reactors. The effect of temperature, cell load and substrate feeding strategy were investigated with controlled continuous stirred membrane bioreactors (CSMR). Amidase enzyme, operated under mild conditions is suitable for the synthesis of labile organic molecules and it is stable up to 50 °C. These batch and CSMR data for enzymatic conversion indicate the potentiality of the continuous bioprocess for industrial application.

Nitto[56,57] discovered the process of selective hydrolysis of nitriles to amides enzymatically and then developed this to include hydrolyzing 3-cyanopyridine to niacinamide. BASF[58] and Lonza[59] have made further developments in this direction. This technology has also been patented for niacinamide process in China.[60] The total hydrolysis of 3-cyanopyridine may be performed by bacterial *nitrilase* from *Acinetobacter, Agrobacterium, Cellulomonas, Microbacterium, Obesumbacterium, Rhodococcus,* at low temperature (5–50 ^{0}C), pH ranging from 4 to 10 and the substrate concentration varying from 10^{-3} to 1 mol L^{-1}. The enzymatic production of nicotinic acid becomes the most efficient alternative. Earlier biosynthesis of nicotinic acid in prototrophs and tryptophan auxotrophs of *Saccharomyces cerevisiae* has been carried out by Ahmad and Moat.[61] According to them, yeasts utilized tryptophan for the synthesis of nicotinic acid under aerobic conditions.

Separation of nicotinic acid

Organic acids, widely used in the food, pharmaceutical and chemical industries, are important chemicals in human life. The fermentation technology for producing organic acids in particular has been known for more than a century, and acids have been produced in the form of aqueous solutions. These bioconversions and recovery from fermentation broth are severely inhibited by the products.

The growing importance of biological production, expressed with new routes and increasing production rates, asks for adapted downstream processing for product separation. Several separation methods such as liquid extraction,[62–64] ultrafiltration,[65] reverse-osmosis,[66] electrodialysis,[65,67–69] direct distillation,[70] liquid surfactant membrane extraction,[71] anion exchange,[72] precipitation and adsorption[73–76] etc. have been employed to remove carboxylic acids.

Nicotinic acid separation is achieved by recovery methods such as spray-drying (especially for veterinary use), crystallization, and thermal decomposition of ammonium nicotinate as against many other methods used for separation of organic acids as mentioned above. Degussa[77] developed a crystallization process to give large nicotinic acid crystals. This involves the total hydrolysis of 3-cyanopyridine with a strong base. Lonza[78] and Nippon Soda[79] utilized the decomposition of ammonium nicotinate at elevated temperatures. Lonza[80] converted highly concentrated solutions of ammonium nicotinate to pure nicotinic acid by spray-drying, which also ensures a free-flowing material. The nicotinic acid can be freed from residual ammonium nicotinate by a thermal post-treatment in a fluidized bed or under reduced pressure. Boreskov[81] developed a process, which incorporates the desublimation of nicotinic acid out of the gas stream. All these separation techniques have severe limitations requiring high energy and material consumptions (elevated temperature and pressure, inert media, organic liquid vapors at high temperature etc.), and depend on the nicotinic acid concentration.

Reactive extraction

Among various available alternatives for simultaneous removal of the product, extraction is often the most suitable.[82–86] Reactive extraction is developed to intensify separation by solvent extraction and represents a connection between chemical (solute and extractant reaction) and physical phenomena (diffusion and solubilization of the system components). Therefore, a reactive extraction method has been proposed to be an effective primary separation step for the recovery of bio-products from a dilute fermentation process.[87–90] Some of the advantages are increased reactor productivity and easy control in reactor pH without requiring base addition. The use of a high-concentration substrate as the process feed reduces process wastes and production costs. This method may also allow the process to produce and recover the fermentation products in one continuous step and reduce the downstream processing load and recovery costs.[91] Reactive extraction strongly depends on various parameters such as the distribution coefficient, degree of extraction, loading ratio, complexation equilibrium constant, types of complexes ($q = 1 : 1$, $2 : 1$, etc.), rate constant (k) of carboxylic acid-extractant reaction, properties of the solvent (extractant and diluent), type of solvent, temperature, pH, acid concentration, etc.[92,93]

The extraction of carboxylic acids is categorized into three groups: (i) acid extraction by solvation with carbon-bonded oxygen-bearing extractants (also inert aliphatic and aromatic hydrocarbons and some of their substituted homologs); (ii) acid extraction by solvation with phosphorus-bonded oxygen-bearing extractants and (iii) acid extraction by proton transfer or by ion pair formation, the extractant being high-molecular mass aliphatic amines.[93] The distribution coefficients of carboxylic acids including nicotinic acid between the aqueous phases and organic phases with only first categorized solvents are very low as shown in Table 1.[95–97]

Organophosphoric derivatives and long-chain, aliphatic amines as given in Table 2 are effective extractants for separation of carboxylic acids from dilute aqueous solution. Generally, these extractants are dissolved in a diluent (an organic solvent that dilutes the extractant). It controls the viscosity and density of the solvent phase. However, the chemical structure of a diluent may have various effects connected with the formation of acid-extractant complexes in the organic phase. The equilibrium behavior has been studied effectively by postulating the formation of various stoichiometric complexes of acid and amine.[98–100] Hence, chemical extraction using organophosphoric solvating agents[96,101–106] and high molecular mass aliphatic amines or amine salts[95,107–117] is efficiently employed to remove the acids from dilute solution.

Due to the insolubility of nicotinic acid in simple organic solvents, its separation by physical extraction with first categorized extractants is impossible. However, its extraction could become possible by adding a phosphoric or aminic extractant into the simple solvent, which could react with nicotinic acid, leading to the formation of a hydrophobic compound. Hence, the chemical structure of nicotinic acid contains an acidic group (COOH) and a basic group (N from the pyridine core). The distribution coefficients of nicotinic acid between the aqueous phases and organic phases with various extractants dissolved in solvents are given in Table 3.[95,96,118–119]

The mechanism of the biosynthetic products separation by reactive extraction is specific to the used extraction system. This extraction can be achieved by means of a chemical reaction between the solute and the extractant of solvation, ion ex-

Table 1 – *Distribution coefficients (K_D) of carboxylic acids between water and organic solvents at 25 °C*

Carboxylic acid	Solvent	K_D	References
nicotinic acid	*n*-heptane	0.012	89
	kerosene	0.011	
	methylisobutyl ketone (MIBK)	0.15	
	chloroform	0.018	
	nitrobenzene	0.011	
	cyclohexanone	0.59	
	cyclohexane	0.015	
	1-octanol	0.35	90
	benzene	0.014	
	toluene	0.015	
propionic acid	*n*-hexane	0.005	91
	cyclohexane	0.006	
	benzene	0.043	
	toluene	0.034	
	xylene	0.03	
	carbon tetrachloride	0.015	
	chloroform	0.11	
	nitrobenzene	0.16	
	diethyl ether	1.75	
	diisopropyl ether	0.80	
	methylisobutyl ketone (MIBK)	2.15	
	cyclohexanone	3.30	
	n-butanol	3.20	
	n-pentanol	2.95	
lactic acid	diethyl ether	0.10	
	diisopropyl ether	0.04	
	methylisobutyl ketone (MIBK)	0.14	
	n-octanol	0.32	
succinic acid	diethyl ether	1.50	
	methylisobutyl ketone (MIBK)	0.19	
	n-butanol	1.20	
fumaric acid	diethyl ether	1.50	
	methylisobutyl ketone (MIBK)	1.40	
maleic acid	diethyl ether	0.15	
	methylisobutyl ketone (MIBK)	0.21	
itaconic acid	diethyl ether	0.35	
	methylisobutyl ketone (MIBK)	0.55	
tartaric acid	diethyl ether	0.03	
	methylisobutyl ketone (MIBK)	0.02	
citric acid	diethyl ether	0.01	
	methylisobutyl ketone (MIBK)	0.09	

Table 2 – *Some important phosphorus- and amine-based extractants*

Extractant category	Extractants	References
Phosphorus-bonded oxygen-bearing extractants	tributyl phosphate (TBP)	95–100
	tributyl phosphine oxide (TBPO)	
	trioctyl phosphine oxide (TOPO)	
	Cyanex@923, mixture of four trialkyl phosphine oxide	
	di-(2-ethylhexyl)-phosphoric acid (D2EHPA)	
High-molecular mass aliphatic amine based extractants	lauryl-trialkylmethylamine (Amberlite LA-2)	101–111
	tri-*n*-octylamine (Alamine 300)	
	tri-iso-octylamine (HOSTAREX A 324)	
	tri-*n*-(octyl-decyl)-amine (Alamine 336)	
	quaternary alkylammonium salt (Aliquat 336)	
	tri-*n*-dodeocylamine	

Table 3 – *Distribution coefficients (K_D) of nicotinic acid between water and extractant/solvent system at 25 °C*

Extractant	Solvent	K_D	References
Alamine 300 (Tri-*n*-octyl amine) with conc., $c = 0.0452$ kmol m^{-3}	*n*-heptane	0.06	89, 112
	kerosene	0.05	
	methylisobutyl ketone (MIBK)	0.60	
	chloroform	0.69	
	nitrobenzene	0.71	
	cyclohexanone	1.67	
	cyclohexane	0.7	
	1-octanol	0.90	
	cyclopentanol	2.091	
Tri-butyl-phosphate	–	0.87	90
Amberlite LA-2 (lauryl-trialkylmethylamine) with mass conc., $\gamma = 60$ g L^{-1}	*n*-heptane	0.098	113
	n-butyl acetate	1.13	
	dichloromethane	3.10	
D2EHPA (di-(2-ethylhexyl)-phosphoric acid) with mass conc., $\gamma = 60$ g L^{-1}	*n*-heptane	0.042	
	n-butyl acetate	0.36	
	dichloromethane	0.71	

change or ion-pair formation type. Due to the solubility of system components in the opposite phase, the chemical reaction can occur either at the interfacial region between the aqueous and organic phase, or in the bulk of aqueous or organic phase. The extraction mechanism of nicotinic acid (HNc) with these extractants can be described by eq. (1), showing interfacial equilibrium with an assumption of participation of n molecules of extractant (E) and one acid molecule in the formation of interfacial compound:

$$\mathrm{HNc(aq)} + n\overline{\mathrm{E}}_{org} \rightleftharpoons \overline{\mathrm{HNcE}_{n(org)}} \qquad (1)$$

The extraction ability is represented by the distribution coefficient. The distribution coefficient, K_D, is calculated using eq. (2).

$$K_\mathrm{D} = \frac{[\overline{\mathrm{HNcE}_{n(org)}}]}{[\mathrm{HNc(aq)}]} \qquad (2)$$

The overbar in eq. (2) refers to the organic phase; [HNc(aq)] and $[\overline{\mathrm{HNc(aq)E}_{n(org)}}]$ symbolize the overall concentrations of nicotinic acid in aqueous and organic phase respectively at equilibrium.

The extraction equilibrium constant, K_E, can be calculated using eq. (3):

$$K_\mathrm{E} = \frac{[\overline{\mathrm{HNcE}_{n(org)}}]}{[\mathrm{HNc(aq)}][\mathrm{E}_{org}]^n} \qquad (3)$$

Nicotinic acid also dissociates under equilibrium in aqueous phase as given by eq. (4):

$$\mathrm{HNc} \rightleftharpoons \mathrm{Nc}^- + \mathrm{H}^+ \qquad (4)$$

The corresponding dissociation constant, K_a is determined with the relationship as given by eq. (5):

$$K_\mathrm{a} = \frac{[\mathrm{Nc(aq)}^-][\mathrm{H}^+]}{[\mathrm{HNc(aq)}]} \qquad (5)$$

The extraction equilibrium constant, K_E, and molecules of extractant, n, can be calculated by analysis of concentrations in aqueous and organic phases at equilibrium.

The distribution of nicotinic acid between water and Alamine 300 (tri-*n*-octylamine) dissolved in various polar and non-polar diluents, was studied at 298 K using a phase volume ratio of $\psi = 1 : 1$ by Senol.[95,118] The cyclic alcohol/amine system yielded the highest synergistic extraction efficiency as shown in Table 3. The strength of complex solvation was found to be reasonably high for halogenated aliphatic hydrocarbons and nitrobenzene, activating mainly the formation of probably (1,1) acid-amine complex. Physical solubility of nicotinic acid in pure diluent alone is remarkably low with a distribution coefficient for cyclopentanol of 0.92 and less for others, as shown in Fig. 3.

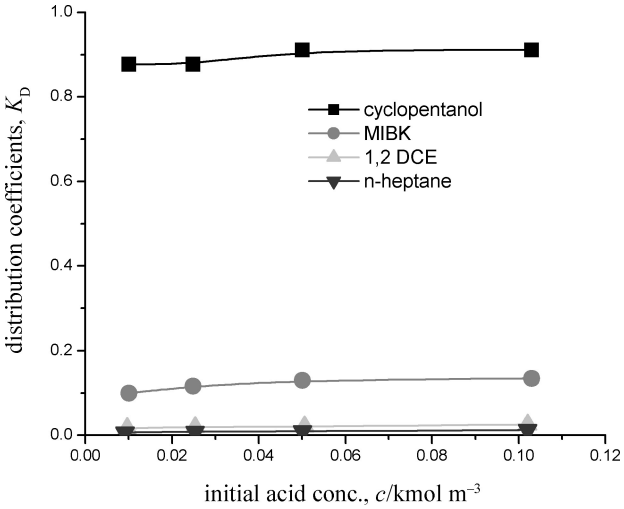


Fig. 3 – *Physical extraction of nicotinic acid (NA) by conventional solvents*[112]

Kumar *et al.*[95] carried out the equilibrium study for recovery of nicotinic acid using reactive extraction. The conventional solvents, such as simple hydrocarbon, ketone, kerosene oil and alcohol have been used with and/or without phosphorous bonded oxygen bearing extractants such as tri-*n*-butyl phosphate (TBP). Effects of nicotinic acid concentration, diluent and extractant composition on distribution are studied. Maximum recovery of nicotinic acid is obtained by dissolving tri-*n*-octyl phosphine oxide (TOPO) in methyl isobutyl ketone (MIBK) at an initial nicotinic acid concentration of $c = 0.105$ kmol m^{-3} as shown in Figs. 4 and 5. In this equilibrium extraction study, solvation numbers and equilibrium constants between water and nicotinic acid are also investigated with both

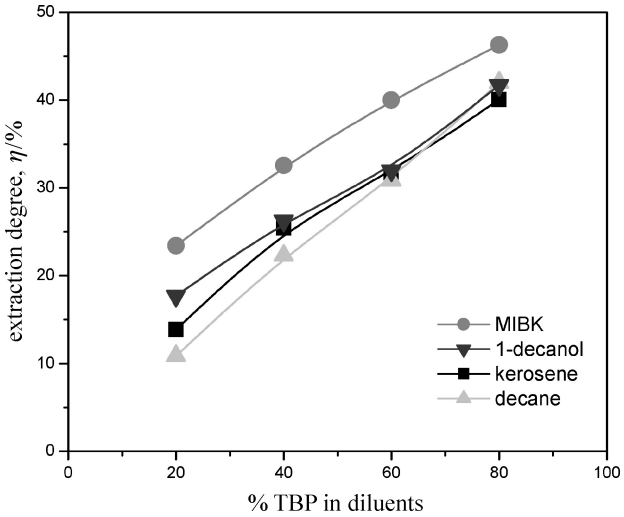
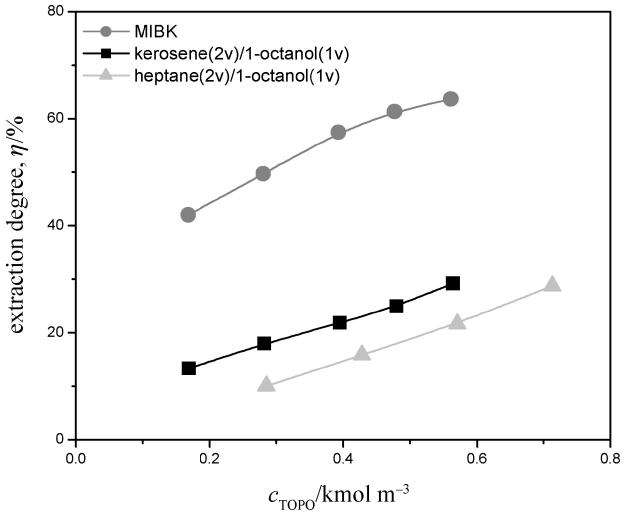
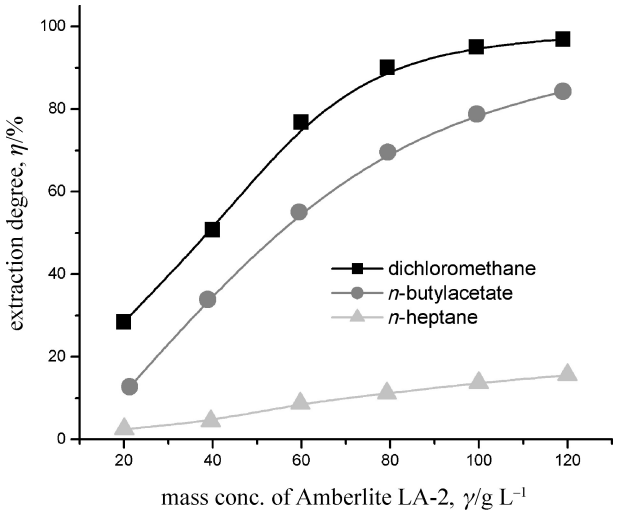


Fig. 4 – *Extraction degree with variation of TBP concentration in various diluents*

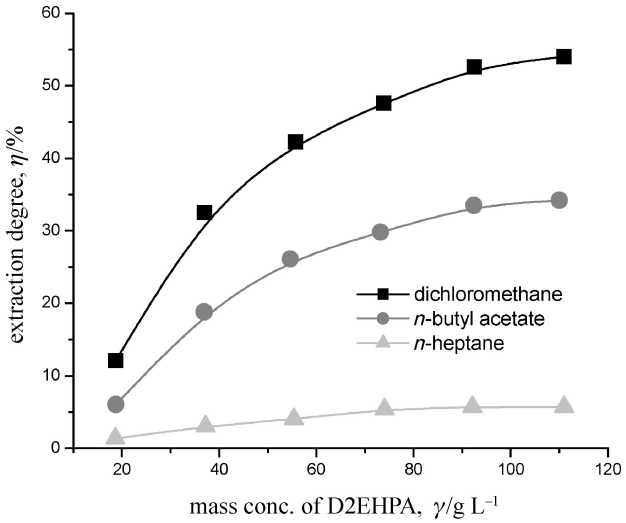


F i g . 5 – *Extraction degree with variation of TOPO concentration in various diluents*



F i g . 7 – *Influence of concentration of amberlite LA-2 on extraction degree of nicotinic acid*[113]

TBP and TOPO.[119] The comparative study of the reactive extraction of nicotinic acid with Amberlite LA-2 (lauryl-trialkyl-methylamine) and di-(2-ethyl-hexyl)-phosphoric acid (D2EHPA) had been presented by Cascaval *et al.*[120] Compared to D2EHPA, the use of Amberlite LA-2 allows the possibility of reaching higher extraction efficiency, the extraction degree being supplementally increased by increasing the solvent polarity as shown in Figs. 6 and 7. The highest value of the extraction constant has been obtained for reactive extraction with Amberlite LA-2 dissolved in dichloromethane (Fig. 7).



F i g . 6 – *Influence of concentration of D2EHPA on extraction degree of nicotinic acid*[113]

Conclusions

Over the last three decades, there has been a resurgence of interest in large-scale production of biochemicals via enzymatic fermentation due to the sharp increase in petroleum cost. Therefore, substantial improvements in the existing recovery technology for fermentation products are required to penetrate the organic and biochemical industries. In the conversion of cyanopyridine to niacin and niacinamide, the enzymatic hydrolysis is a new development, which offers several advantages over the established chemical processes. It is important to have an efficient and sustainable process for the intensification of nicotinic acid separation. Commercial processes such as spray-drying and crystallization etc. for nicotinic acid separation are based on corresponding high energy and material consumption. However, the reactive extraction technique presents a very attractive research domain for biochemical and biotechnological engineers. The studies on reactive extraction of nicotinic acid with aminic and phosphoric extractants in various solvents have opened new avenues in the production of nicotinic acid via enzymatic conversion. Equilibrium study at various extractant concentrations and pH values of aqueous solutions indicate that the reactive extraction occurs by means of the interfacial reaction of hydrogen bonding or ionic type. Conventional solvents are not suitable separation agents for nicotinic acid, yielding distribution coefficient $K_D < 1$. The extraction efficiency is improved using amine-based extractants with active diluents.

Future scope

The growing demand of nicotinic acid draws attention to the intensification of nicotinic acid production via enzymatic conversion. Extractive fermentation seems to be more promising since it is very simple and easy to scale up. However, two major obstacles are to be overcome. The first one is the organic solvent toxicity towards the microorganisms for the extraction, and the second is the difference in the pH optima for fermentation and extraction. In view of this, there is an urgent need to develop extractants that work at higher pH or strains that yield good conversion to nicotinic acid at lower pH. There is a lot of scope to generate the reactive extraction data with less toxic or non-toxic amine and phosphorus-based extractants and diluents. These equilibrium data will be useful in the design of extraction processes for the intensification of nicotinic acid production. There is a need to carryout research on this in particular at different isothermal conditions with mixed extractants and diluents to estimate the factors modifying the regeneration stage. Reactive extraction using aminic and phosphoric extractants is an emerging prospective method for the recovery of nicotinic acid.

List of symbols

c – concentration, mol L^{-1}
k – rate constant
K_D – distribution coefficient
K_E – equilibrium constant
K_a – dissociation constant
n – number of molecules
q – number of acid molecules per extractant molecules
r – mole ratio
γ – mass concentration, g L^{-1}
η – extraction degee, %
ψ – volume ratio

References

1. *Brody, T.,* Nutritional Biochemistry, 2nd Ed., Academic Press, San Diego, 1999.
2. *Shils, M., Olson, J. A., Shike, M., Ross, A. C.,* Nutrition in Health and Disease, 9th Ed., Williams & Wilkins, Baltimore, 1999.
3. *Gregory, J. F.,* Ann. Rev. Nutr. **18** (1998) 277.
4. *Cervantes, L. D., McElvaney, N. G., Moss, J.,* Niacin. In: *Shils, M., Olson, J. A., Shike M., Ross A. C.,* (Eds.), Modern Nutrition in Health and Disease, 9th ed. Williams & Wilkins, Baltimore, 1999.
5. *Jacobson, M. K., Jacobson, E. L.,* Trends Biochem. Sci. **24** (11) (1999) 415.
6. *Jacobson, E. L., Jacobson, M. K.,* Methods Enzymol. **280** (1997) 221.
7. *Hendler, S. S., Rorvik, D. R.,* (Eds.) PDR for Nutritional Supplements. Medical Economics Company, Inc, Montvale, 2001.
8. *Jacob, R., Swenseid, M., Niacin.* In: *Ziegler, E. E., Filer, L. J.,* (Eds.) Present Knowledge in Nutrition. 7th ed. ILSI Press, Washington D. C., 1996, p185.
9. *Katzung, Bertram, G.,* Basic and clinical pharmacology, McGraw-Hill Medical Publishing Division, New York, 2006.
10. *Canner, P. L., Berge, K. G., Wenger, N. K.,* J. Am. Coll. Cardiol. **8** (6) (1986) 1245.
11. Niacin abuse in the attempt to alter urine drug tests. Pharmacist's Letter/Prescriber's Letter, 23(6) (2007) 230606.
12. Food and Nutrition Board, Institute of Medicine. Niacin. Dietary Reference Intakes, National Academy Press, Washington, D.C., 1998, p123.
13. *Park, Y. K., Sempos, C. T., Barton, C. N., Vanderveen, J. E., Yetley, E. A*., Am. J. Public Health **90** (2000) 727.
14. *Boyonoski, A. C., Spronck, J. C., Gallacher, L. M.,* J. Nutr. **132** (2002) 108.
15. *Jacobson, E. L.,* J. Am. Coll. Nutr. **12** (2000) 412.
16. *Negri, E., Franceschi, S., Bosetti, C.,* Selected micronutrients and oral and pharyngeal cancer. Int. J. Cancer **86** (2000) 122.
17. *Franceschi, S., Bidoli, E., Negri, E.,* Int. J. Cancer **86** (2000) 626.
18. *Jacobson, E. L., Shieh, W. M., Huang, A. C.,* Mol. Cell. Biochem. **193** (1-2) (1999) 69.
19. *Lampeter, E. F., Klinghammer, A., Scherbaum, W. A.,* Diabetes **47** (1998) 980.
20. *Greenbaum, C. J., Kahn, S. E., Palmer, J. P.,* Diabetes **45** (11) (1996) 1631.
21. *Schatz, D. A., Bingley, P. J.*, J. Pediatr. Endocrinol. Metab. **14** (1) (2004) 619.
22. *Knopp, R. H.,* N. Engl. J. Med. **341** (1999) 498.
23. *Cheung, M. C., Zhao, X. Q., Chait, A., Albers, J. J., Brown, B. G.,* Arterioscler. Thromb. Vasc. Biol. **21** (2001) 1320.
24. *Brown, B. G., Zhao, X. Q., Chait, A.,* N. Engl. J. Med. **345** (2001) 1583.
25. *Murray, M. F., Langan, M., MacGregor, R. R.,* Nutrition **17** (2001) 654.
26. *Tang, A. M., Graham, N. M., Saah, A. J.,* Am. J. Epidemiol. **143** (1996) 1244.
27. Ullmann's Encyclopedia of Industrial Chemistry. 5th Ed. A27 (1995) 581.
28. *Galaction, A. I., Cascaval, D.,* Secondary Metabolites with Pharmaceutical, Cosmetic and Food Applications; Venus: Iasi, Romania, 2006.
29. *Chuck, R.,* Appl. Cat. A.: General **280** (2005) 75.
30. Ullmann's Encyclopedia of Industrial Chemistry, 5th Ed. A22 (1993) 399.
31. *Lukas, V. H., Neher, A., Arntz, D.,* (Degussa AG, Germany) EP 726,092, 14 Aug 1996.
32. *Saito, M., Tsukahara, K., Yamada, K., Imai, H.,* (Mitsubishi Gas Chemical Co., Inc., Japan), EP 339,680, 2 Nov 1989.
33. *Dicosimo, R., Burrington, J. D., Grasselli, R. K.,* (Standard Oil Co., USA) US 5,028,713, 2 Jul 1991.
34. *Luecke, B., Martin, A., Seeboth, H., Ladwig, G., Parlitz, B., French, J.,* DD 241,903, 7 Jan 1987.

35. *Suvorov, B. V., Sembaev, D. Kh., Afanas'eva, T. A., Tolmacheva, T. P., Saurambaeva, L. I., Gostev, V. I., Kan, I. I., Glubokovskikh, L. K.,* (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R., USSR) SU 1,014,228, 28 Feb 1991.
36. *Narayana, K. V., Masthan, S. K., Rao, V. V., Raju, B. D., Rao, P. K.,* Catal. Commun. **3** (4) (2002) 173.
37. *Manohar, B., Reddy, B. M.,* J. Chem. Technol. Biotechnol. **71** (2) (1998) 141.
38. *Cislak, F. E., Wheeler, Wm. R.,* (Reilly Tar and Chemical Corp.) GB 563,274, 8 Aug 1944.
39. *Chuck, R. J., Zacher, U.,* (Lonza AG, Switzerland.) EP 919,548, 2 Jun 1999.
40. *Asamidori, Y., Hashiba, I., Takigawa, S.,* (Nissan Chem. Ind. Ltd., Japan) JP 9,426,603, 1994.
41. *Watanabe, H., Hirai, S., Terada, M.,* (Daicel Chemical Industries, Ltd., Japan) JP 2,002,053,556 19 Feb 2002.
42. *Hashimoto, T., Nakamura, K., Takagawa, M.,* (Mitsubishi Gas Chemical Co., Inc., Japan) JP 09,202,772, 5 Aug 1997.
43. *Hashimoto, T., Nakamura, K., Takagawa, M.,* (Mitsubishi Gas Chemical Co., Inc., Japan) JP 08,311,030, 26 Nov 1996.
44. *Hatanaka, M., Tanaka, N.,* (Nissan Chemical Industries, Ltd., Japan) WO 9,305,022, 18 Mar 1993.
45. *Cao, W., Kattau, R. A., Kreilis, G.,* (Reilly Industries, Inc., USA) US 5,756,750, 26 May 1998.
46. *Grendze, M., Vorhies, S. L.,* (Reilly Industries, Inc., USA) WO 0,005,211, 3 Feb 2000.
47. *Beschke, H., Dahm, F. L., Friedrich, H., Prescher, G.,* (Degussa-Huels AG, Fed. Rep. Germany) EP 45,079, 3 Feb 1982.
48. *Beschke, H., Dahm, F. L., Friedrich, H., Prescher, G.,* (Degussa-Huels AG, Fed. Rep. Germany) EP 45,080, 3 Feb 1982.
49. *O'Reilly, C., Turner, P. D.,* J. Appl. Microbiol. **95** (2003) 1161.
50. *Asano, Y., Yasuda, Y., Tani, Y., Yamada, H.,* Agric. Biol. Chem. **46** (1982) 1183.
51. *Mathew, C. D., Nagasawa, T. T., Yamada, H., Kobayashi, M.,* Appl. Environ. Microbiol. **54** (4) (1988) 1030.
52. *Peter, A. V., Christopher, J. K., Peter, S. J. C.,* Enzyme Microb. Technol. **11** (1989) 815.
53. *Qadreyah, A. A., Don A. C.,* Enzyme Microb. Technol. **25** (1999) 718.
54. *Kaplan, O., Vejvoda, V., Plíhal, O., Pompach, P., Kavan, D., Fialová, P., Bezouška, K., Macková, M., Cantarella, M., Jirku, V., Kren, V., Martínková, L.,* J. Appl. Microbiol. Biotechnol. **73** (2006) 567.
55. *Maria, C., Laura, C., Alberto, G., Roberta, I., Ondřej, K., Agata, S., Ludmila, M.,* Enzyme Microb. Technol. **42** (2008) 222.
56. *Yamada, H., Nagasawa, T.,* (Nitto Chemical Industry Co., Ltd., Japan) EP 307,926, 22 Mar 1989.
57. *To, F., Fujita, C.,* (Nitto Chemical Industry Co., Ltd., Japan) JP 03,280,891 11 Dec 1991.
58. *Ress-Loeschke, M., Hauer, B., Mattes, R.,* (BASF AG, Germany) DE 10,010,149, 6 Sep 2001.
59. *Robins, K. T., Nagasawa, T.,* (Lonza AG, Switzerland) WO 9,905,306, 4 Feb 1999.
60. *Heveling, J., Armbruster, E., Utiger, L., Rohner, M., Dettwiler, H.-R., Chuck, R. J.,* (Lonza AG, Switzerland) EP 770,687, 2 May 1997.
61. *Ahmad, F., Moat, A. G.,* J. Biol. Chem. **241** (4) (1966) 775.
62. *Hauer, E., Marr, R.,* Int. Chem. Eng. **34** (2) (1994) 178.
63. *Wardell, J. M., King, C. J.,* J. Chem. Eng. Data. **23** (1978) 144.
64. *Baniel, A. M.,* EP 0,049,429, 1982.
65. *Boyaval, P., Corre, C., Terre, S.,* Biotechnol. Let. **9** (3) (1987) 207.
66. *Timmer, J. K. M., Kromkamp, J., Robbertsen, T.,* J. Membr. Sci. **92** (1994) 185.
67. *Hongo, M., Nomura, Y., Iwahara, M.,* Appl. Environ. Microbiol. **52** (2) (1986) 314.
68. *Nomura, Y., Iwahara, M., Hongo, M.,* Biotechnol. Bioeng. **30** (1987) 788.
69. *Lee, E. G., Moon, S., Chang, Y. K., Yoo, I., Chang, H. N.,* J. Membr. Sci. **145** (1998) 53.
70. *Cockrem, M. C. M., Johnson, P. D.,* U.S. Patent 5,210,296, 1991.
71. *Sirman, T., Pyle, D. L., Grandison, A. S.,* Biochem. Soc. Trans. **19** (3) (1991) 274.
72. *Cao, X., Yun, H. S., Koo, Y. M.,* Biochem. Eng. J. **11** (2002) 189.
73. *Dai, Y., King, J.,* Ind. Eng. Chem. Res. **35** (1996) 1215.
74. *Pazouki, M., Panda, T.,* Bioprocess Eng. **19** (1998) 435.
75. *Kawabata, N., Yasuda, S., Yamazaki, T.,* US patent 4,323,702, 1982.
76. *Chen, C. C., Ju, L. K.,* Appl. Microbiol. Biotechnol. **59** (2002) 170.
77. *Moeller, A., Friedrich, H. Kuhn, Winkler, H. K.,* (Degussa-Huels AG, Fed. Rep. Germany) DE 3,614, 019, 5 Nov 1987.
78. *Chuck, R. J., Zacher, U.,* (Lonza AG, Switzerland) EP 919,548, 2 Jun 1999.
79. *Hayakawa, K., Hatayama, M.,* (Nippon Soda Co., Ltd., Japan) WO 9,900,350, 7 Jan 1999.
80. *Chuck, R. J., Zacher, U.,* U S Patent 6,376,677, 2002.
81. *Andrushkevich, T. V., Makarenko, M. G., Prokhorov, V. P., Vasilev, E. V., Zenkovets, G. A., Al'kaeva, E. M., Ginevich, G. I.,* (Boreskova Inst Kataliza Sibir) RU21097341-998, 27 April 1998.
82. *Chauhan, R. P., Woodley, J. M.,* Chemtech. **27** (1997) 26.
83. *Freeman, A., Woodley, J. M., Lilly, M. D.,* Biotechnol. J. **11** (1993) 1007.
84. *Jaquet, A., Quan, L., Marison, I. W., Stockar, U. V.,* J. Biotechnol. **68** (1999) 185.
85. *Jaquet, A., Quan, L., Meyer, H.-P., Stockar, U. V.,* Chimia **50** (1996) 427.
86. *Weilnhammer, C., Blass, E.,* Chem. Eng. Technol. **17** (1994) 365.
87. *Wennersten, R.,* J. Chem. Technol. Biotechnol. **33B** (1983) 85.
88. *Hartl, J., Marr, R.,* Separ. Sci. Technol. **28** (1993) 805.
89. *Cascaval, D., Galaction, A. I.,* Chem. Ind. **58** (9) (2004) 375.
90. *Ye, K., Jin, Sh., Shimizu K.,* J. Ferment. Bioeng. **81** (1996) 240.
91. *Wasewar, K. L., Yawalkar, A., Moulijn, J., Pangarkar, V. G.,* Ind. Eng. Chem. Res. **43** (2004) 5969.
92. *Kahya, E., Bayraktar, E., Mehmeto, G. U.,* Turk. J. Chem. **25** (2001) 223.
93. *Yang, S., White, S. A., Hsu, S.,* Ind. Eng. Chem. Res. **30** (1991) 1335.

94. *Kertes, A. S., King, C.,* Biotechnol. Bioeng. **28** (1986) 269.
95. *Senol, A.,* Chem. Eng. J. **83** (3) (2001) 155.
96. *Kumar, S., Vibhuti, A., Babu, B. V., Wasewer, K. L.,* Proceedings of International Symposium & 59th Annual Session of IIChE (CHEMCON-2006), Bharuch, December 27-30, 2006.
97. *Schugeri, K.,* Solvent Extraction in Biotechnology, Springer-Verlag, Berlin, 1994.
98. *Tamada, J. A., Kertes, A. S., King, C. J.,* Ind. Eng. Chem. Res. **29** (7) (1990) 1319.
99. *Tamada, J. A., Kertes, A. S., King, C. J.,* Ind. Eng. Chem. Res. **29** (7) (1990) 1327.
100. *Tamada, J. A., Kertes, A. S., King, C. J.,* Ind. Eng. Chem. Res. **29** (7) (1990) 1334.
101. *Hano, T., Matsumoto, M., Ohtake, T., Sasaki, K., Hori, F., Kawano, Y. J.,* Chem. Eng. Jap. **23** (1990) 734.
102. *Malmary, G., Faizal, M., Albet, J., Molinier, J.,* J. Chem. Eng. Data. **42** (1997) 985.
103. *Wang, Y., Li, Y., Wang, J., Li, Z., Dai, Y.,* J. Chem. Eng. Data **46** (2001) 831.
104. *Cai, W., Zhu, S., Piao, X.,* J. Chem. Eng. Data **46** (2001) 1472.
105. *Al-Mudhaf, H. F., Hegazi, M. F., Abu-Shady. A. I.,* Sep. Pur. Technol. **27** (2002) 41.
106. *Wisniewski, M., Pierzchalska, M.,* J. Chem. Technol. Biotechnol. **80** (2005) 1425.
107. *Cascaval, D., Onisco, C., Hung, J.,* J. Ind. Chem. **25** (1997) 245.
108. *Matsumoto, M., Takagi, T., Nakaso, T., Kondo, K.,* Solv. Extr. Res. Dev. Jpn. **6** (1999) 144.
109. *Jung, M., Schierbaum, B., Vogel, H.,* Chem. Eng. Technol. **23** (2000) 70.
110. *Cascaval, D., Onisco, C., Hung, J.,* J. Ind. Chem. **28** (2000) 99.
111. *Malmary, G., Albet, J., Putranto, A. M. H., Molinier, J.,* Brazil. J. Chem. Eng. **18** (4) (2001) 441.
112. *Wasewar, K. L., Heesink, A. B. M., Versteeg, G. F., Pangarkar, V. G.,* J. Biotechnol. **97** (2002) 59.
113. *Hong, Y. K., Hong, W. H.,* Korean J. Chem. Eng. **21** (2) (2004) 488.
114. *Yankov, D., Molinier, J., Albert, J., Malmary, G., Kyuchoukov, G.,* Biochem. Eng. J. **21** (2004) 63.
115. *Mariya, M., Joel, A., Jacques, M., George, K.,* Ind. Eng. Chem. Res. **44** (2005) 6534.
116. *Wasewar, K. L., Pangarkar, V. G.,* Chem. Biochem. Eng. Q. **20** (3) (2006) 325.
117. *Kumar, S., Babu, B. V., Wasewer, K. L.,* Proceedings of International Symposium & 59th Annual Session of IIChE (CHEMCON-2006), Bharuch, December 27-30, 2006.
118. *Senol, A.,* Turk. J. Chem. **26** (2002) 77.
119. *Kumar, S., Wasewar, K. L., Babu, B. V.,* Chem. Eng. Technol. **31** (11) (2008) 1.
120. *Cascaval, D., Galaction, A. I., Blaga, A. C., Camarut, M.,* Sep. Sci. Technol. **42** (2007) 1.