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Multiphase catalytic reactor engineering and design for pharmaceuticals and fine chemicals

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Abstract

A review of recent developments in multiphase catalytic processes for the manufacture of pharmaceutical and fine chemicals, and an overview of reaction engineering principles needed for analysis of the local and overall reaction rate for reactor design and interpretation of performance is presented. The first section gives an overview of recent applications in pharmaceuticals and fine chemicals where heterogeneous and homogeneous catalyzed multiphase chemistries have been identified that are more efficient and represent safer operation with decreased environmental impact when compared to existing processes. The next three sections describe a scheme for classification of the various types of reactions that are typically encountered, along with distinguishing features of these reactions and commonly used multiphase reactor types. This is followed by a review of reaction engineering principles needed for describing the local overall rate of reaction, including a summary of typical models for evaluation of the intrinsic reaction kinetics, incorporation of transport-kinetic interactions, methods for identification of the controlling reaction regime and assessment of the relative contribution of transport effects. The next two sections set forth basic reactor models for commonly used reactor types, including mechanically agitated reactors and bubble column reactors. A brief summary of commonly used correlations for estimation of mass transfer coefficients in these reactors for gas–liquid and liquid–liquid systems is also given. The final section is devoted to a summary of key reaction engineering issues that occur in pharmaceutical and fine chemical multiphase catalytic processes, along with some thoughts on future needs and challenges.

Keywords: Reactor; Multiphase; Design; Scale-up

1. Introduction and scope

Chemical processes used to manufacture pharmaceuticals, specialty chemicals and fine chemicals often involve the production of high value-added products with an annual basis of a few kilograms to several thousand metric tons. These processes are chemistry intensive, and very often involve products with complex structures that must meet high purity requirements and stringent product specifications for very specific applications. Conventional processes used in industry for the manufacture of pharmaceuticals are largely based on stoichiometric organic synthesis, but these lead to large quantities of by-products consisting of inorganic salts that now pose a serious waste disposal problem. The focus in earlier days was more

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on quality of the final products, even though the overall yield to the desired product in many situations was very poor. This was acceptable practice due to the large difference between the selling price and manufacturing cost of these products. For example, suppose that the gross sales of an average pharmaceutical product are about \$US 250×10^6 per year based upon an annual production rate of 15 000 kg. This suggests that the apparent selling price is \$167 000 per kg. Since the difference between the selling price and manufacturing cost is at least 50%, then it is evident that low yields could be tolerated while still making a good profit. For this reason, issues related to reactor design and environmental needs were considered to be on a low priority. However, in recent years, more stringent environmental regulations and increasing competition has resulted in the development of new processes where catalysis and reactor design have gained increasing attention. Replacement of less attractive stoichiometric routes with newer routes based on catalysis is an obvious solution to the problems of eliminating hazardous and environmentally unacceptable processes for specialty chemicals. Many important discoveries in catalysis in recent years have revolutionized conventional pharmaceutical processes, and the potential of catalysis in newer applications is even greater. Some important examples include: (1) a new process for the manufacture of ibuprofen [1] involving catalytic hydrogenation and carbonylation steps; (2) hydroxylation of phenol to hydroquinone and catechol using ZSM-5 catalyst; (3) auto-oxidation of *para*-diisopropylbenzene to hydroquinone; (4) oxidative carbonylation of methanol to dimethyl carbonate; (5) asymmetric hydrogenation of acetamido-cinnamic acid derivatives for L-dopa and L-phenylalanine using chiral homogeneous catalysts; and (6) hydrogenation of a variety organic compounds containing different functional groups. All of these catalytic routes provide more economical and environmentally benign processes.

Most pharmaceutical, specialty and fine chemical catalytic processes involve liquid phase reactions with gas, liquid or solid phase reactants and soluble homogeneous or solid heterogeneous catalysts. Multiphase reaction engineering aspects relevant to processes in pharmaceuticals and fine chemical industries have been reviewed by Mills et al. [2], while the general literature on this subject is also summarized in the books by Doraiswamy and Sharma [3] and Ramachandran and Chaudhari [4]. Some specific examples of reactor engineering aspects are also analyzed by Paul [5] and Wiederkehr [6]. The analysis and design of reactors for pharmaceuticals and specialty products is generally complex, which is mainly due to the changing transport and thermodynamic properties of the system and their subsequent influence on heat and mass transport, mixing of the various fluid phases and complex reaction kinetics, including side reactions that lead to undesired products. In addition, heat effects, control of reaction temperature and the effect of these variables on selectivity and product quality are also important.

The primary objective of this paper is to provide an overview of multiphase reaction engineering with an emphasis upon catalytic processes in pharmaceuticals and specialty chemicals. In the first section, a review of specific routes and processes for pharmaceuticals and specialty chemicals is provided where soluble organometallic or solid heterogeneous catalysts are employed to yield a particular product. Distinguishing features and classification of the various reaction types that are encountered in practice are also discussed. The next section provides an overview of specific multiphase reactor types that are most often used in these application areas. This is followed by a discussion on modeling of reaction networks from the perspective of intrinsic kinetic models. Next, a review of local mass transfer effects for gas–liquid, gas–liquid–liquid and gas–liquid–solid, and controlling reaction regimes is given. The final sections discuss integral reactor models and specific design cases. Finally, conclusions and future needs in this area are discussed.

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2. Application areas

Multiphase catalytic reactions have played an important role in the development of new processes for pharmaceuticals, fine chemicals and specialties. In this section, a brief review of important applications and examples is presented along with classification of

reaction types and their distinguishing features from a reactor design point of view.

Classification of multiphase reaction processes for pharmaceuticals, specialty and fine chemicals can generally be performed using two methods: (1) classification based upon the mode of utility of the reactants and the type of phases involved, such as gas–liquid, gas–liquid–solid, liquid–solid, gas–liquid–liquid and gas–liquid–liquid–solid reactions and (2) classification depending on the process chemistry or type of catalysis involved. The first method is more convenient for analysis of reactor design issues, while the second method is more useful for describing the process routes, since each of the examples will belong to one of the categories in (1). In either case, the final applications of these multiphase processes occur in the manufacture of products for agrochemicals, pharmaceuticals, detergents, dyestuffs, perfumery and fragrances, feed additives, flavors and food products, polymers, textiles and synthetic fibers. In the following sections, examples of selected applications that mainly involve homogeneous or heterogeneous catalytic processes that have made significant impact in recent years are discussed.

2.1. *Heterogeneous catalytic reactions*

A wide variety of reactions encountered in processes for pharmaceuticals and fine chemicals involve the use of solid catalysts, such as supported metals and metal oxides, zeolites and heteropolyacids. Specific applications of these are reviewed by Sheldon [7], Mills et al. [2], Kozhevnikov [8], Dartt and Davis [9] and Gilbert and Mercier [10]. Most of these can be categorized as gas–liquid–solid or liquid–solid reactions where the solid is a heterogeneous catalyst. The important reaction classes include: (1) hydrogenation; (2) oxidation; (3) alkylation; (4) reductive amination; (5) hydroxylation; (6) isomerization; (7) acylation; and (8) oxidative carbonylation. Here, a few important reactions from these classes are described that have replaced conventional stoichiometric processes while providing cleaner technologies with less environmental impact because of reduced production of wastes and by-products.

An important example of how catalytic reaction steps can lead to processes with minimum waste generation and energy consumption is a new route developed by Hoechst for ibuprofen, which is an anti-inflammatory non-steroidal drug. A comparison between the new catalytic route and the conventional organic synthetic route is given in Fig. 1. This new route involves only three catalytic steps, while the conventional process is a six-step synthesis producing stoichiometric quantities of various inorganic salts, typically on a one-to-one molar basis. In the second step, selective hydrogenation of *p*-isobutyl acetophenone to *p*-isobutyl phenyl ethanol is an example of a gas–liquid–solid catalytic reaction that is usually carried out in a slurry reactor. During hydrogenation, side reactions leading to the formation of *p*-isobutyl styrene, *p*-isobutyl ethyl benzene and various ether derivatives occur so that selectivity is an important issue. Supported palladium (Pd), nickel (Ni) and ruthenium (Ru) catalysts have been proposed as selective hydrogenation catalysts. In the presence of an appropriate alkali base metals, selectivity to the desired *p*-isobutyl phenyl ethanol product is favored.

Liquid-phase selective catalytic hydrogenation is often encountered in the pharmaceutical and specialty chemical industries. Selected examples are summarized in Table 1.

Referring to Table 1, hydrogenation of nitro-aromatics to amines is a commonly used process for a number of key chemical intermediates and fine chemicals [32]. For example, hydrogenation of 2,4-dinitrotoluene (DNT) to toluene diamine (TDA) is an important step in the manufacture of TDI (toluene diisocyanate), which is a monomer used in the production of polyurethane. The stoichiometric reactions involved are given in Fig. 2. This is an example of a multistep, three-phase catalytic reaction with high exothermicity, and it is carried out in a mechanically agitated slurry reactor using supported Pd or Ni catalysts. Selective conversion of DNT to TDA and temperature control are important issues in this process.

Hydrogenation of halo-nitrobenzenes, such as *m*-nitrochlorobenzene to *m*-chloroaniline using a sulfided-supported Pt catalyst in a slurry reactor, is important in the manufacture of the antimalarial drug chloroquine and amodiquin. These catalytic hydrogenation processes eliminate the problems of handling Fe–HCl sludge in the conventional reduction process. They also give high quality products and are more economical.

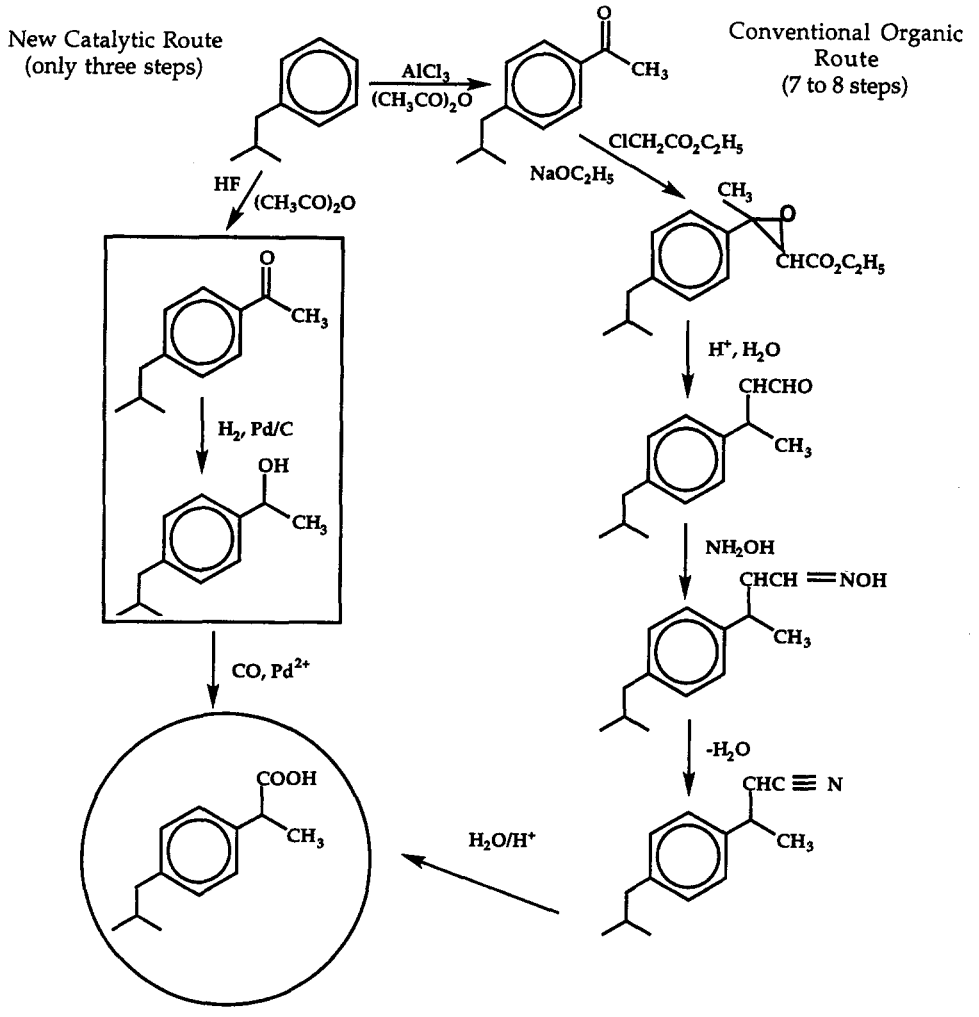
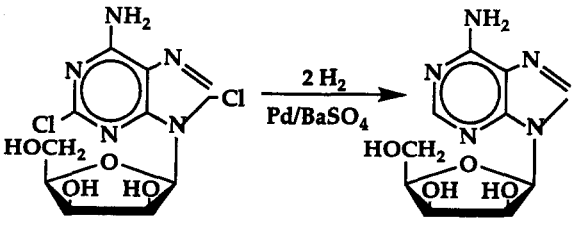


Fig. 1. New catalytic route to ibuprofen (after Sheldon [11]).

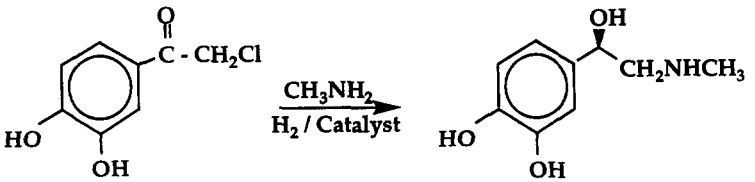
Some selected examples of catalytic hydrogenation in the synthesis of drugs or intermediates with complex structures are given below:



(2.1)

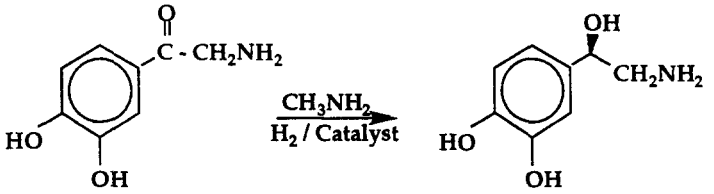
1. Hydrogenation of 2,8-dichloroadenosine to adenosine, which is a neuro-regulatory drug, is conducted in the presence of a $Pd/BaSO_4$ catalyst [19].

2. Reductive amination of catechol derivatives to adrenaline and noradrenaline



(-) Adrenaline

(2.2)



4-amino acetyl catechol Noradrenaline

(2.3)

Table 1
Examples of gas–liquid–solid catalytic reactions

Reaction	Catalyst	Product (application)	Reference
1. Hydrogenation of glucose	Raney Ni	Sorbitol (pharmaceuticals)	[12]
2. Hydrogenation of 2,4-dinitrotoluene	Pd/alumina or Raney Ni	Toluenediamine – an intermediate for TDI (fine chemicals)	[13]
3. Hydrogenation of *o*, *m* and *p*-nitrochlorobenzenes	Pt/C – sulfided	Chloroanilines (pharmaceuticals and dyes)	[14,15]
4. Hydrogenation of *o*-nitroanisole	Pd/C	*o*-Anisidine (dyes, fine chemicals)	[16]
5. Hydrogenation of butynediol	Pd–Zn/$CaCO_3$	*cis*-Butenediol, an intermediate for vitamin A and endosulfan (pesticide)	[17]
6. Hydrogenation of *p*-isobutylacetophenone	Pd/C, Ni/HYZeolite	*p*-Isobutylphenylethanol intermediate in ibuprofen – a drug (pharmaceuticals)	[18,81]
7. Hydrogenation of 2,8-dichloroadenosine	Pd/$BaSO_4$	Adenosine, a neuro-regulatory drug (pharmaceuticals)	[19]
8. Reductive amination of 4-chloroacetylcatechol	Pd/support	Adrenaline – a drug (pharmaceuticals)	[20]
9. Hydrogenation of fluoro methyl acetylene derivative of methylphenyl sulfone	Pd/$CaCO_3$	Florfenicol – an antibacterial drug (pharmaceuticals)	[21]
10. Hydrogenation of 4-aminoacetylphenol	Pd/support	Octopamine – a drug (pharmaceuticals)	[22]
11. Hydrogenation of adiponitrile	Raney Ni	Hexamethylene diamine (HMDA) – intermediate for Nylon 6,6 (specialty chemicals)	[23]
12. Hydrogenation of 1,5,9-cyclododecatriene	Pd/Al_2O_3	Cyclododecene – an intermediate for 12-laurolactam (pharmaceuticals)	[24,25]
13. Hydrogenation of cinnamaldehyde	Pt–Co/C or Pt–Ru/C	Cinnamyl alcohol (fine chemicals, perfumery)	[26]
14. Hydrogenation of 3-hydroxypropanal	Ni-support	1,3-Propanediol (fine chemicals)	[27]
15. Hydrodesulfurization of *o*-aminobenzyl sulfides, 2-methyl (trimethyl-6-trifluromethylaniline)	Co-molybdate on Al_2O_3	2-Methyl-6-trifluoromethyl aniline (MTMA) – a pre-emergent herbicide intermediate (specialty agrichemicals)	[28]
16. Ethnylation of formaldehyde	Cu-acetylide-Bi-silica gel	Butynediol (fine chemicals and pharmaceuticals)	[29]
17. Oxidation of glucose	Pd–Bi/C	Glutonic acid (food, detergents and pharmaceuticals)	[30,31]

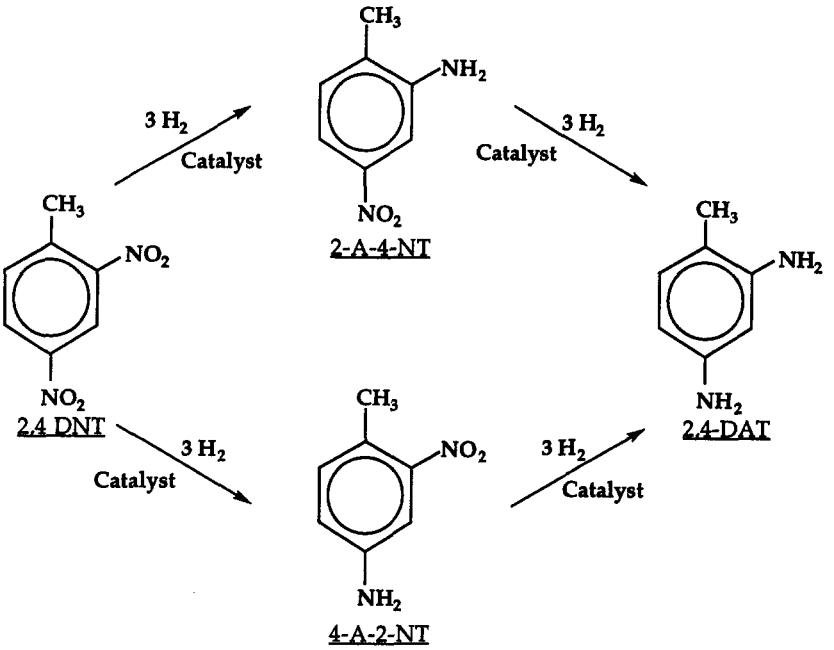
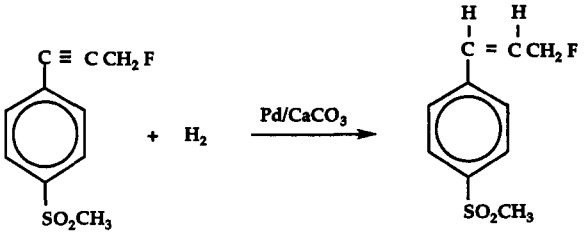
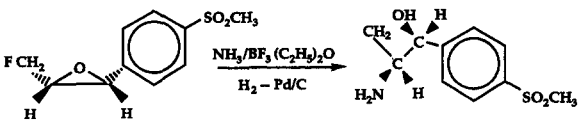


Fig. 2. Reaction scheme for hydrogenation of 2,4-dinitrotoluene (2,4-DNT). 2-A-4-NT=2-amino-4-nitrotoluene; 4-A-2-NT=4-amino-2-nitrotoluene; 2,4-DAT=2,4-diaminotoluene.

3. Synthesis of florfenicol, which is an antibacterial drug, involves the following hydrogenation reactions as intermediate steps:

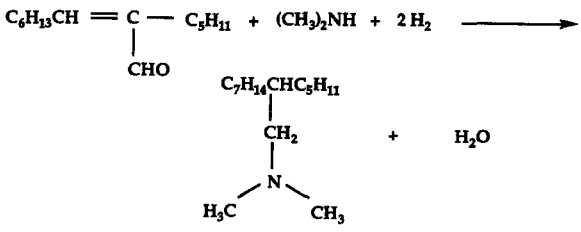


(2.4)



(2.5)

An interesting example of a three-phase catalytic hydrogenation in specialty chemicals processes is the reductive amination of long-chain C_{14} unsaturated, branched aldehydes with dimethylamine and hydrogen to the corresponding saturated branched amine derivatives. These reaction products are intermediates to long chain amine oxides, which are used in the manufacture of light-duty detergents for residential and commercial applications [33,34]. The stoichiometric reactions are:



(2.6)

The above reaction is performed in a mechanically agitated slurry reactor using a Pd-on-carbon at 373 K and 3551 kPa of hydrogen pressure. Various amine products can be produced by use of other primary, secondary and tertiary amines.

A non-phosgene route for the manufacture of carbamates and isocyanates via oxidative carbonylation of amines provides another recent application of gas–liquid–solid reactions in specialty chemicals. One important example is the oxidative carbonylation of methyl amine to *N*-methyl-methylcarbamate (MMC), which occurs by the following primary reaction:

$$2CH_3NH_2 + 2CO + O_2 \xrightarrow[\text{Catalyst}]{2CH_3OH} 2CH_3NHCOOCH_3 + 2H_2O \quad (2.7)$$

(MMC)

MMC is condensed with α-naphthol to obtain carbaryl insecticide. This is a non-phosgene, non-MIC route for carbamate insecticides that eliminates the hazards in handling of phosgene and methyl isocyanate, which led to the Bhopal tragedy in the early 1980s in the conventional process.

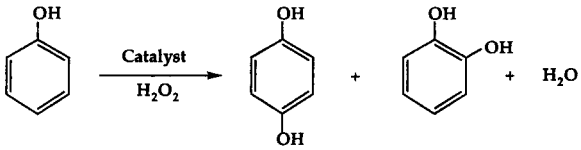
Another important example is the oxidative carbonylation of aniline to phenylurethane. This reaction is an important step in the new non-phosgene process for methylene diphenyl diisocyanate (MDI), developed by Asahi Chemicals. The overall stoichiometry is

$$2C_6H_5NH_2 + 2CO + O_2 \xrightarrow[\text{Catalyst}]{2C_2H_5OH} 2C_6H_5NHCOOC_2H_5 + 2H_2O \quad (2.8)$$

(Phenylurethane)

Both the production of MMC via Eq. (2.7) and MDI via Eq. (2.8) are reactions that involve simultaneous absorption of two gases (CO and O_2) which is followed by a reaction with a liquid reactant (aniline or methyl amine) in the presence of a suspended powdered catalyst. The primary and secondary reactions are highly exothermic and hence control of temperature and the gas phase O_2 concentration in the system are important design problems from a safety perspective, in addition to selectivity aspects.

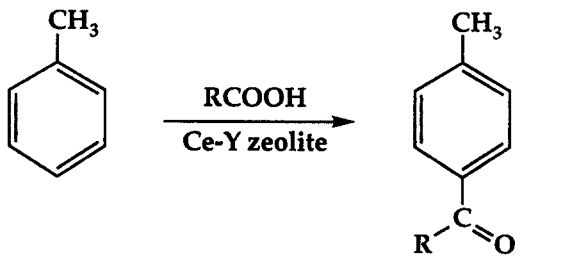
Numerous examples of liquid–solid catalytic reactions are encountered in the manufacture of specialty chemicals. A partial summary is provided in Table 2. The most important developments in recent years are hydroxylation reactions using zeolites as catalysts. Hydroxylation of phenol using ZSM-5 or TS-1 type catalyst with hydrogen peroxide gives hydroquinone with catechol as a co-product [39].



(2.9)

The use of hydrogen peroxide, although expensive when compared to molecular oxygen, is preferred because it is simpler and safer to use. This is an example of a liquid–solid catalytic reaction where nearly 99% selectivity to the dihydroxybenzenes is achieved. This route is also very attractive from an environmental point of view, since the conventional route using Fenton's reagent (Fe salt+H_2O_2), produces about 10 kg of salts for each kilogram of product. In the catalytic route, very little salt is produced and the lowest molar ratio of by-product catechol to hydroquinone is obtained.

Other examples of liquid–solid catalytic reactions occur in the acylation of aromatic compounds and in various condensation reactions. As illustrated in Eq. (2.10), acylation of alkyl benzene with carboxylic acids in the presence of a modified catalyst facilitates the synthesis of aromatic ketones, which are intermediates in certain pharmaceuticals and perfumery chemicals.



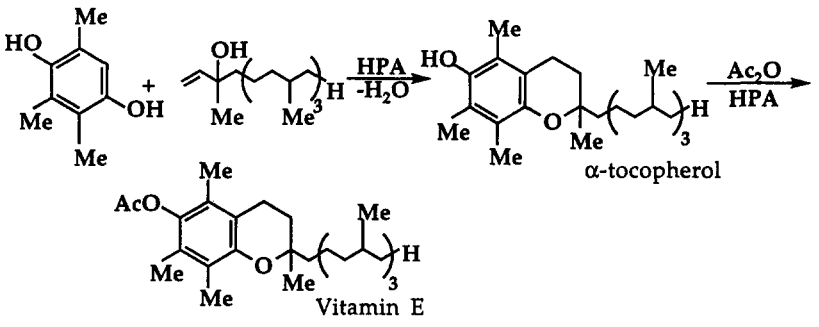
(2.10)

The above catalytic route is a major development, since the conventional route uses stoichiometric quantities of metal chlorides ($AlCl_3$) along with acid

Table 2
Examples of liquid–solid catalytic reactions

Reaction	Catalyst	Product (application)	Reference
1. Hydroxylation of phenol with H_2O_2	Ti-silicate (TS-1)	Hydroquinone and catechol (fine chemicals and pharmaceuticals)	[35]
2. Condensation of isophytol with 2,3,5-trimethyl hydroquinone	Heteropolyacids PW/SiW	α-Tocopherol (vitamin E) (pharmaceuticals)	[8]
3. Epoxidation of styrene followed by isomerization	Ti-silicate (TS-1)	Phenylacetaldehyde (fine chemicals)	[36]
4. Isomerization of safrol	Na/Al_2O_3	Isosafrol (flavors and perfumery)	[37]
5. Acylation of substituted benzenes with carboxylic acids	Ce–Y or HZSM-5	Aromatic ketones (substituted) (fine chemicals)	[38]
6. Reaction of *o*-xylene and *t*-butyl-2,6-dialkylphenols	Heteropolyacids	*t*-Butylxylenes (pigments)	[8]
7. Esterification of dipicolinic acid with butanol	Cesium-promoted heteropolyacid	Dibutyl dipicolinate (pharmaceuticals)	[8]

chlorides, which lead to severe environmental problems. Conversely, the use of catalysis provides a simple, clean process with minimum waste products. However, the indicated catalysts are effective only for some derivatives and are not generic in their applicability to acylation reactions.



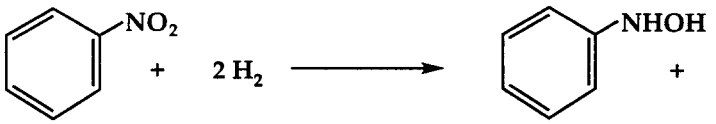
(2.11)

Heteropolyacids as catalysts for fine chemicals and pharmaceuticals manufacture have been recently reviewed by Kozhevnikov [8], which suggests that great potential exists for developing new, economical and environmentally benign processes. For example, condensation of isophytol and 2,3,5-trimethylhydroquinone to α-tocopherol and subsequent acetylation is catalyzed by heteropolyacids to produce vitamin E. The chemistry of these complex molecules is

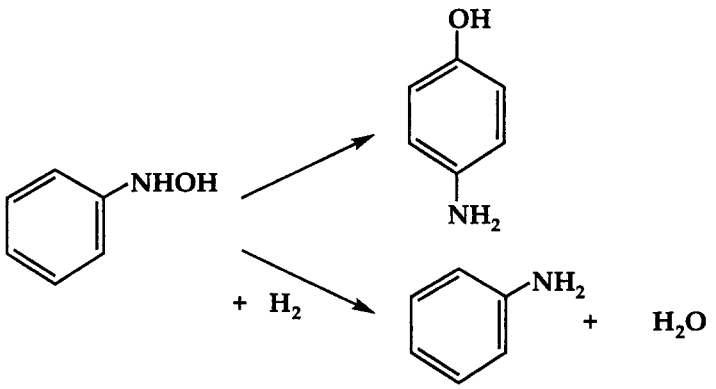
These reactions involve liquid–solid contacting that produce high quality product with improved yields. The formation of waste products is also nearly eliminated, which is unlike the conventional process where H_2SO_4 or $ZnCl_2$ catalysts are used.

A few cases of gas–liquid and liquid–solid catalytic reactions are also noteworthy in the manufacture of pharmaceuticals. A detailed review of this particular category of multiphase reactions is omitted due to brevity. A well-known example of this class is the

hydrogenation of nitrobenzene to *p*-aminophenol, which is an intermediate for drug Paracetamol. The reactions given below form the basis for a process developed by Mallinkrodt.



(2.12a)



(2.12b)

The above hydrogenation reactions are carried out using either a Pt/C or PtO catalyst in the presence of aqueous H_2SO_4. The intermediate phenyl hydroxylamine is formed in the organic phase and is rearranged to *p*-aminophenol in the presence of H_2SO_4. Further hydrogenation of phenyl hydroxylamine to aniline competes with the rearrangement and hence selectivity is a key issue in this process.

2.2. *Homogeneous catalytic reactions*

Catalysis by soluble metal complexes is used extensively in pharmaceuticals, fine chemicals and specialties. The two important factors that would increase the development and application of homogeneous catalysis in these areas include: (1) increased competition in the pharmaceutical industry, along with a need for selective, efficient and environmentally acceptable processes; and (2) new homogeneous catalysis that can produce biologically active molecules with asymmetric centers that allow precise control of chirality [40]. Commercial applications of homogeneous catalysis in these product areas have been extensively reviewed in a series of papers by Parshall and Nugent [41,42,43] to which the reader is referred for details. Some important examples are summarized in Tables 3 and 4 for reference.

Applications of homogeneous catalysis have mainly emerged in three categories: (1) gas–liquid reactions, such as carbonylations, hydroformylations and oxidations; (2) perfumery chemicals; and (3) intermediates for pharmaceuticals.

An illustration is the carbonylation of ethanol to propionic acid and its ester, which finds application as a food preservative. The stoichiometric reaction is

$$C_2H_5OH + CO \xrightarrow[HI\ or\ LiI]{Rh\ or\ Ni\ complex} C_2H_5COOH \qquad (2.13)$$

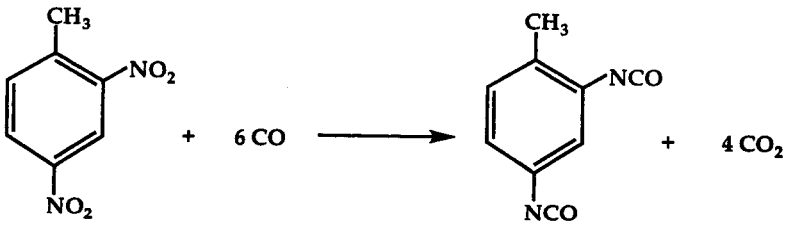
This reaction is performed in an agitated gas–liquid reactor or a bubble column reactor using a homogeneous Rh [54] or Ni-isoquinoline catalyst [55,66] at 230°C and 7000 kPa CO pressure.

Shown in (2.14) below is another example of this reaction class is the carbonylation of 2,4 dinitrotoluene to toluene diisocyanate (TDI), which is an

Table 3
Examples of gas–liquid reactions using homogeneous catalysis

Reaction/process	Catalyst	Product (application)	Reference
1. Selective hydrogenation of C-22/C-23 double bond in synthesis of ivermectin	$Rh(I)Cl(PPh_3)_3$	Ivermectin – antiparasitic drug (pharmaceuticals)	[44]
2. Hydrocyanation of bicyclo(2,2,1)-5-heptene-2-carbonitrile followed by hydrogenation	$Ni(OPPh)_4$–$ZnCl_2$–$OPPh_3$	Diaminomethylnorbonone (NBDA) – hardener for epoxy resin (fine chemicals)	[45]
3. Condensation of aniline and ethylene glycol to indole with H_2 evolution	PbI/BaI_2 or $CdBr_2$/KBr	Indole – an intermediate for indigo – dye stuff (fine chemicals)	[46]
4. Oxidation of indole to indigo	Cumyl hydroperoxide	Indigo – a dye stuff	[47,48]
5. Hydrogenation of maleic anhydride to butyrolactone	$Ru(acac)_2$ phosphine complex	Butyrolactone (fine chemicals)	[49]
6. Hydrogenation of dehydrolinalool		Linalool (fine chemicals, perfumery)	[41,42,43]
7. Hydroformylation of 1,4-diacetoxybutene	$HRh(CO)(PPh_3)_3$ or Rh complex without PPh_3	4-acetoxy-2-methyl crotonaldehyde – an intermediate in vitamin A (pharmaceuticals)	[50]
8. Ethylation of aniline	Al-trianilide	2,6-diethylaniline – an intermediate for Dual™ herbicide (agrichemicals)	[51]
9. Hydroformylation of acrylonitrile	Co–carbonyl complex	$NC(CH_2)_2$ CHO – an intermediate for sodium glutamate (food products)	[52]
10. Reaction of isobutylene and ethyl diazoacetate with N_2 evolution	Chiral Cu-complex	+1*S*-2,2-dimethylcyclopropane carboxylic acids – an intermediate for cilastathm (pharmaceuticals)	[53]
11. Carbonylation of ethanol	Rh–carbonyl complex or Ni–isoaquinoline/LiI complex	Propionic acid – in food prservative/perfumery (fine chemicals)	[54,55]
12. Hydroformylation of 1-decene	$HRh(CO)(PPh_3)_3$	Undecanal (perfumery)	[56]
13. Carbonylation of 2,4-dinitrotoluene	$Pd(Py)_2Cl_2$ or $Rh(Py)_3Cl_3$	Toluene diisocyanate (TDI) – intermediate for polyurethane (specialty chemicals)	[57]
14. Carbonylation of nitrobenzene	$Pd(Py)_2Cl_2$ or $Rh(Py)_3Cl_3$	Phenyl urethane – intermediate for MDI (specialty chemicals)	[58]
15. Carbonylation of *p*-nitrocumene	$Pd(Py)_2Cl_2$ or $Rh(Py)_3Cl_3$	*p*-Cumyl isocyanate – intermediate in pesticide – isoproturan (fine chemicals)	[59]
16. Carbonylation of 1,4-diacetoxy butane	Rh–carbonyl iodide complex	Adipic acid (specialty chemicals)	[54]
17. Oxidation of *p*-*t*-butyl toluene	Co complex – Br promoted	*p*-*t*-Butylbenzaldehyde (fine chemicals and perfumery)	[60]

intermediate for polyurethane foams.



(2.14)

This process involves a high pressure gas–liquid reaction with desorption of CO_2 and is catalyzed by $Pd(Py)_2Cl_2$ or $Rh(Py)_3Cl_3$ at 200°C and 8000–9000 kPa pressure [57]. This single step process provides an important alternative to the phosgene route, the latter of which involves three steps and handling of toxic materials and corrosive by-products.

Table 4
Examples of asymmetric catalysis in pharmaceuticals and fine chemicals

Reaction	Catalyst	Product (application)	Category	Reference
1. Hydrogenation of acetamido cinnamic acid (3-methoxy-4-acetoxy derivative)	Rh–DIPAMP chiral complex	L-Dopa (pharmaceuticals)	G–L–S	[61]
2. Asymmetric hydrogenation of α-acetamidocinnamic acid	$[Rh(PNNP)(NBD)]^+$ – a chiral complex	L-Phenylalanine (foods, pharmaceuticals)	G–L	[62]
3. Asymmetric hydrogenation of 2-naphthyl-4-methoxyacrylic acid	Ru–BINAP – chiral complex	*S*-Naproxen (pharmaceuticals)	G–L	[63]
4. Synthesis of α-tocopherol by asymmetric hydrogenation	Ru–BINAP	Vitamin E (pharmaceuticals)	G–L	[64]
5. Hydrogenation of 4-acetoxyzetidine-2-one derivative	Ru–BINAP	β-LACTAM (pharmaceuticals)	G–L	[64]
6. Isomerization of diethylgeranylamine	Rh(*S*)–BINAP	Citronellal diethylamine, vitamin E and menthol (pharmaceuticals and perfumery)	Homogeneous	[65]
7. Hydrogenation of 4-phenyl 2-oxoethylbutyrate	Modified Raney-Ni	Enalapoil (pharmaceuticals)	G–L–S	[35]

G-L: Gas–liquid; G–L–S: Gas–liquid–solid.

A new process developed by Enichem for dimethyl carbonate (DMC) via oxidative carbonylation of methanol is a recent example of homogeneous catalysis that eliminates use of toxic phosgene. DMC is a valuable intermediate for polycarbonates and carbamate insecticides that occurs according to the following main reaction:

$$4CH_3OH + 2CO + O_2 \rightarrow 2(CH_3O)_2CO + 2H_2O \quad (2.15)$$

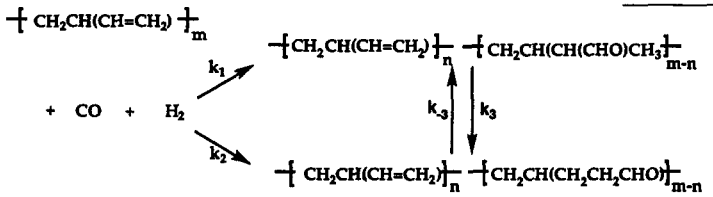
The reaction is performed at 120°C and 2500 kPa using a mixture of O_2 and synthesis gas along with a soluble Cu complex catalyst. This is an example of simultaneous absorption of two gases with reaction in the liquid phase. Control of the reactor temperature and the O_2 concentration in the system are critical factors in reactor design and operation. It is generally preferred to operate the reactor for oxidative carbonylation with either complete consumption of O_2, or under conditions of O_2 starvation for safety reasons.

Hydroformylation of olefinic substrates is an important class of homogeneous catalytic reaction for the synthesis of saturated and unsaturated aldehydes. These aldehydes typically serve as intermediates and building blocks for a variety of products, such as alcohols, amines, alcohol ethoxylates, carboxylic acids and other derivatives, that have applications in pharmaceuticals, fine chemicals and perfumery chemicals. An excellent review on this subject has been recently given by Beller et al. [67]. Although hydroformylation has found extensive applications in commodity chemicals, such as in the synthesis of oxo alcohols for plasticizers and detergents, this section summarizes some recent examples where it has been used in certain specialty and pharmaceutical chemical applications.

Intermediate to long-chain aldehydes having seven to eleven carbons as commonly used in perfumery chemicals are produced by hydroformylation of C_6–C_{10} olefins [68]. Similarly, a new process for vitamin A involves hydroformylation of 1,4-diacetoxybutene to produce 4-acetoxymethyl crotonaldehyde using a homogeneous Rh complex catalyst [69]. Similarly, hydroformylation of acrylonitrile using a soluble cobalt complex catalyst yields cyano-propionaldehyde. This latter reaction is an intermediate step in the manufacture of sodium-glutamate, which is an important food additive [52].

An interesting and useful application of hydroformylation in specialty chemicals is found in the functionalization of low molecular weight olefinic polymers. Hydroformylation of either 1,4-polybuta-

diene or 1,2-polybutadiene using $HRhCO(PPh_3)_3$ catalyst with excess PPh_3 gives high selectivity to the corresponding 1,4 and 1,2 substituted polyaldehydes [70].



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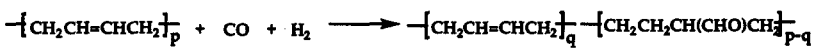
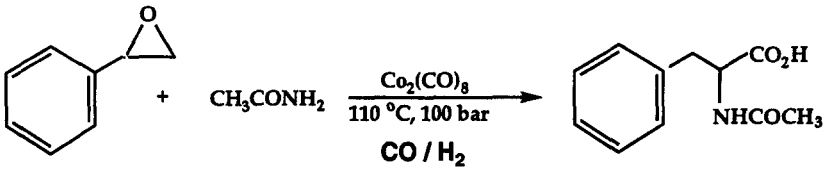


Homogeneous catalytic oxidation of hydrocarbons is also extensively used in pharmaceuticals and fine chemicals. Various applications have been recently reviewed by Sheldon [35] and Kozhevnikov [8]. The main catalysts used are metal oxides, salts and heteropolyacids. An excellent example is the manufacture of 2-methyl-1,4-naphthoquinone by oxidation of 2-methylnaphthalene using a soluble heteropolyacid catalyst [8].

This is an important step in the manufacture of vitamin K, and provides a cleaner process alternative to the traditional stoichiometric oxidation carried out using $K_2Cr_2O_7$.

A new route for manufacture of indigo dyes by the oxidation of indole is a recent example reported by Mitsui Toatsu Chemicals where a soluble cumyl hydroperoxide catalyst is used [46].

A new class of reactions involving amidocarbonylation of aldehydes using homogeneous catalysis provides an alternative to the conventional Strecker synthesis based on toxic NaCN or HCN to produce amino acids. An important example is the amidocarboxylation of styrene oxide to L-phenylalanine [71], which is the key intermediate for the synthetic sweetener aspartame. This reaction involves styrene oxide and acetamide as liquid reactants with CO/H_2 as gas phase reactants. The stoichiometric reaction is



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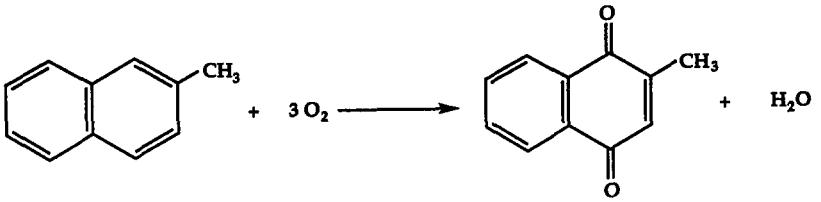

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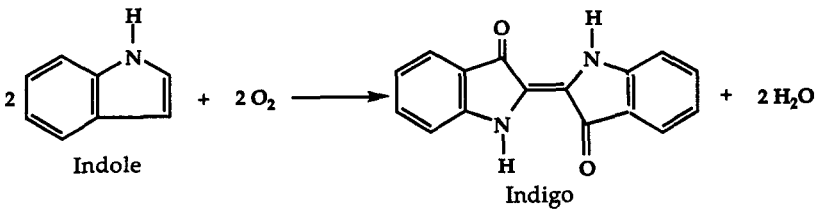
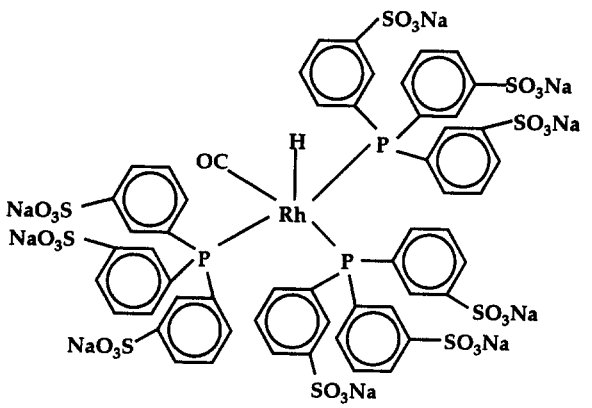


(2.19)

This reaction is carried out using homogeneous dicobalt octacarbonyl precursor along with Ti-isopropoxide as a catalyst at 110°C and 100 bar.

Although homogeneous catalytic processes have made a significant impact on different synthetic routes due to their high selectivity under relatively milder operating conditions, a major drawback of these systems has been the difficulty in separation and development of economical methods for the reuse of the often expensive catalysts. In this context, a major development in recent years has been the use of water soluble catalysis in a biphasic medium and the use of phase transfer catalysis. Important features of the biphasic catalytic reactions have been reviewed by Kalck and Monteil [72], Herrmann and Kohlpaintner [73] and Chaudhari et al. [74]. Some important applications in fine chemicals and pharmaceuticals are given by Beller et al. [67]. In this section, the selected biphasic catalytic reactions involving gas–liquid–liquid contacting and their applications are discussed. Also, some significant conceptual developments in this area and classification of biphasic catalytic reactions are also highlighted.

Hydroformylation of C_6–C_{10} olefins using a water soluble Rh complex catalyst with triphenyl phosphine trisulfonate (TPPTS) ligand is an important example of this class of reactions. The end products are important as perfumery chemicals [68,74]. In this case, the Rh-TPPTS catalyst is highly soluble in the aqueous phase, while reactants and products remain in the organic phase and hence the catalyst recycle is easily achieved by phase separation. A typical structure of the water soluble Rh catalyst for hydroformylation is



(2.20)

In this system, the reaction occurs in the aqueous phase and hence the rate of reaction is limited by the solubility of the olefin and gaseous reactants in water. Thus, in spite of the advantage of an easy catalyst/product separation, the overall efficiency of the process is significantly lower than conventional homogeneous catalysts. In this context, several attempts have been made to design new biphasic systems using one of three different approaches: (1) a co-solvent to solubilize the reactants in water; (2) supported aqueous phase catalysis (SAPC) in which the liquid–liquid contact area is increased by supporting a thin film of water soluble catalyst on silica [75]; and (3) promoted interfacial catalysis where catalyst binding ligands or water soluble surface active ligands are used [74]. As illustrated in Fig. 3, the concept of promoting interfacial catalysis leads to approx. 50–100 times enhancement of the hydroformylation rate for 1-octene.

Other examples are found in the teleomerization of butadiene using water soluble Pd-triphenyl phosphine monosulfonate (TPPMS) catalyst and hydroformylation of unsaturated C_8 aldehydes to C_9 dialdehydes using $Rh(acac)(CO)_2$–TPPMS catalyst. These steps are important in a process developed by Kuraray Corporation for C_9 diol that have end-applications in plasticizers [67].

The new route for ibuprofen as illustrated earlier in Fig. 1 involves carbonylation of *p*-isobutyl phenyl

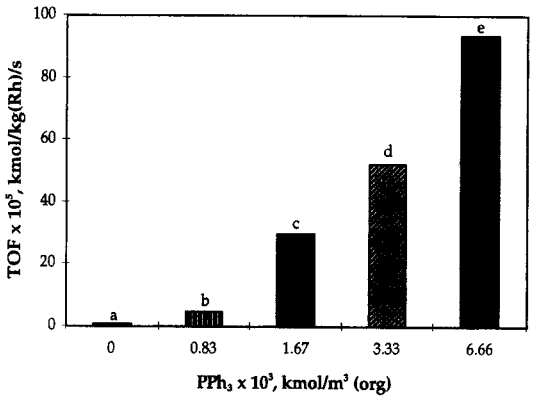
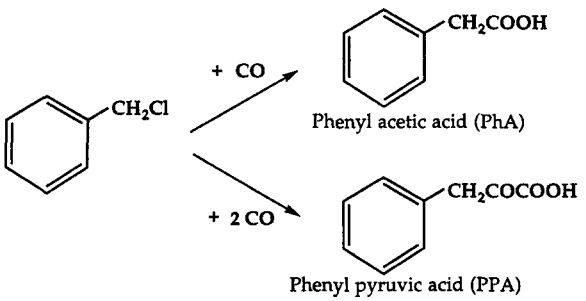


Fig. 3. Effect of the PPh_3 catalyst binding ligand concentration on the turnover frequency for the hydroformylation of 1-octene. Reaction conditions: $[Rh(COD)Cl]_2$=0.01 kmol/m^3 (aqueous phase); T=373 K, $\bar{p}_{CO}$=2.07 MPa; $\bar{p}_{H_2}$=2.07 MPa; [1-octene]=0.85 kmol/m^3 (organic phase); [TPPTS]=0.12 kmol/m^3 (aqueous phase); agitation speed=900 rpm; aqueous phase holdup=0.4; solvent system=toluene–water; total volume of aqueous+organic phases=2.5×10^{-5} m^3 (After Chaudhari et al. [74]).

ethanol using a soluble Pd complex catalyst in the presence of aqueous HCl as a promoter. This system is biphasic, since it involves two immiscible liquid phases where the organic phase contains the catalyst and reactants, while the aqueous phase contains the promoter.

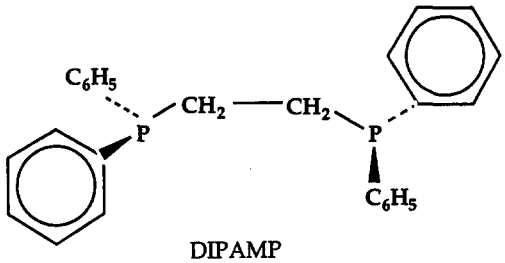
A commercial example of a biphasic catalytic reaction is the carbonylation of benzyl chloride using an organometallic catalyst with a phase transfer agent. This reaction is used in the manufacture of phenyl acetic acid, which is an intermediate for Penicillin G. The stoichiometric reactions involved are:



(2.21)

In this process, the carbonylation reaction occurs in the organic phase, whereas the products are recovered in the aqueous phase as the salts of phenyl acetic acid and phenyl pyruvic acid. A phase transfer catalytic agent facilitates transport of the catalyst precursor from the aqueous to the organic phase, and the catalytic cycle operates through reactions in the bulk of both phases and at the liquid–liquid interface. The selectivity of the two products is strongly dependent on pressure such that at a lower pressure of CO (<1500 kPa), the selectivity to phenyl acetic acid is favored. Conversely, the selectivity to phenyl pyruvic acid increases with an increase in CO pressure. PPA is an important intermediate in the manufacture of the amino acid L-phenylalanine.

A major impact of homogeneous catalysis in pharmaceuticals has been in the manufacture of optically active and stereo selective compounds. Some important examples are found in asymmetric hydrogenation, isomerization and hydroformylation reactions. Asymmetric hydrogenation of acetamido cinnamic acid-3-methoxy, 4-acetoxy derivative using Rh-DIPAMP chiral complex catalyst is an important step in the manufacturing of L-dopa, which is a drug for the treatment of Parkinson's disease.



DIPAMP

(2.22)

Another example of this class is the asymmetric hydrogenation of α-acetamidocinnamic acid using a $[Rh\text{-}(PNNP)(NBD)]^+$ chiral catalyst for the manufacture of L-phenylalanine. This latter molecule is an intermediate for the synthetic sweetener, aspartame.

Other examples of asymmetric catalysis in pharmaceuticals and specialty products are summarized in Table 4. These reactions often involve liquid–solid or gas–liquid–solid reactions with the principle reaction taking place in the liquid phase. The solid phase usually consists of sparingly soluble reactants or products. For example, in the asymmetric hydrogenation of the acetamidocinnamic acid derivative for the synthesis of L-dopa, the reactant is sparingly soluble in the reaction medium and the desired product precipitates in the system. The catalyst and racemic products remain in the solution. Thus, this complexity must be carefully considered in designing reactors for this or other related reactions having similar characteristic features.

3. Classification of reactions

The various types of chemical reactions that occur in the processes described in Section 2 for pharmaceuticals and fine chemicals can be classified depending on the number and type of phases present, and the type of catalyst used. This classification is essential before the interaction between transport effects and kinetics can be analyzed using reaction engineering principles, and before the problems of reactor design and scale-up can be understood and quantified.

A detailed presentation of multiphase reaction classification is given in the review of Mills et al. [2]. Heterogeneous catalytic reactions can be classified into the categories of gas–liquid–solid, liquid–solid, or gas–liquid–liquid–solid reactions where the catalyst is present as a solid phase with reactants and products as gas and liquid phases. For homogeneous catalyzed reactions, the catalyst is usually totally soluble in the liquid phase and the reactions can be classified into the categories of gas–liquid, liquid–liquid and gas–liquid–liquid reactions. A few cases of gas–liquid–solid reactions with reactants and possibly products present as a solid phase are found in asymmetric catalysis. Here, the catalyst is present in the liquid phase and the dissolution of the gas and solid reactants with reaction occurs simultaneously. These classifications can be used to characterize most pharmaceutical and fine chemical processes. Each category has some distinguishing features in these processes due to complexities that occur due to variable transport and thermodynamic properties of the reaction media, sensitivity of the product quality to reaction and process conditions, and the properties of the mixing and mass transfer characteristics of the particular multiphase systems. Some important distinguishing features are given in the following section.

4. Distinguishing features

The important distinguishing features of multiphase reactions and processes that occur in fine chemicals and pharmaceuticals are listed below:

1. The reactants and products in pharmaceuticals applications often have very complex structures and are non-volatile. Production of the desired products at very high conversion and selectivity is critical, since traditional separation technology often is not practical or feasible. In many cases, stereoselective conversion is desirable, since the resulting isomers have different physical properties that sometimes allow straightforward separations.
2. The reactions often involve complex multistep synthesis whose intermediates and products affect system properties and reaction kinetics. Products are often sensitive to changes in reaction conditions, especially pH and reaction temperature. Sometimes, the intermediates and products are thermally unstable and can decompose with moderate variation in conditions from specified mean values.
3. Typical pharmaceutical processes involve an average of about eight reaction steps. Owing to the large number of steps, these are characterized by a relatively low overall yield when compared to conventional chemical or petroleum processes that involve two or three reaction steps. For example, assume that each step of an eight step process has 100% conversion and 90% selectivity to give a yield of 90%. The overall process yield for all eight steps is only 43%. Even though the efficiency of each step is quite high, the overall yield is less than 50%. Generally, the overall yield can be significantly less since the yield of the individual steps is often less than 90%.
4. Most processes involve multiphase catalytic reactions with gas and liquid phase reactants with solid or soluble catalysts so that interphase mass transfer and mixing of fluid phases can influence the overall rate of reaction. Due to non-ideal properties of the system, such as ionic media or polar solvents, the usual correlations for mass and heat transport parameters in the literature developed for ideal mixtures or air–water may not be valid in processes for pharmaceuticals. The effect of temperature on side reactions, quality of products, viscosity and other key transport coefficients, solubility of reactants and products, and phase equilibrium is more complex in these processes.
5. In most cases, batch or semi-batch reactors are used because production rates are small and a single reactor system may be used for many products. In some cases, continuous operation may be mandatory for reasons dictated by the scale of production, economics, kinetics and safety. For example, in reactions with gaseous co-products or those with substrate inhibited kinetics, continuous operation or semi-continuous addition of reactants may be necessary. Some processes require continuous removal of products due to their adverse effect on catalyst activity, their unstable nature under extreme reaction conditions, or thermodynamic equilibrium.

6. In processes involving asymmetric catalysis, precise control of reaction conditions is often necessary as a slight change in these may affect the enantio-selectivity of the desired product.
7. Heterogeneous or soluble organometallic catalysts used are often very expensive and high efficiencies of separation of these from the non-volatile products can pose a major challenge. In addition, catalyst activity and stability over prolonged batch cycles can decrease significantly. Finally, catalysts are not recycled in most pharmaceutical processes due to the possibility of impurity accumulation on product contamination. The impact of catalyst replacement on overall manufacturing economics must be carefully considered.

5. Multiphase reactor types

The reactor types that can be used for multiphase catalytic reactions generally depend on the particular reaction classification and the type of phases involved. Reactor selection and design for gas–liquid, gas–liquid–solid, liquid–liquid, gas–liquid–liquid and liquid–solid systems is an important consideration for processes in fine chemicals and pharmaceuticals. In this section, a brief overview of the principle reactor types, their modes of operation, novel designs and general considerations when selecting a particular reactor type in the context of processes in pharmaceuticals and fine chemical is presented.

Detailed descriptions of the different types of reactors, including their advantages and disadvantages along with scale-up considerations, are given by Mills et al. [2] and Chaudhari et al. [59]. Included in this discussion are factors to consider when selecting a laboratory-scale multiphase reactor for discrimination between kinetic rate equations using kinetic parameter estimation.

A specific example of reactor design for specialty chemicals has been illustrated by Paul [5] for a liquid–liquid reaction involving acid or base catalyzed hydrolysis in the synthesis of the parenteral antibiotic primaxin. Considering the various aspects of reaction engineering and their implications in product selectivity and purity, a novel reactor design having a combined reactor–extractor function was proposed. As shown in Fig. 4, the final device was a Podbielmak

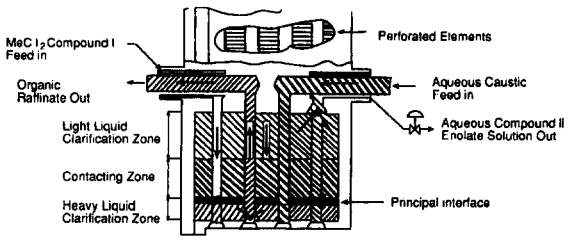


Fig. 4. Podbielmiak centrifugal extractor/reactor for a liquid–liquid reaction in the synthesis of antibiotic Primaxin® (after Paul [5]).

centrifugal extractor. This type of reactor provides very high interfacial area between the two reacting phases while also providing the necessary residence time to accomplish the process objectives.

Another example of using reaction engineering concepts for process improvement with a novel reactor in the manufacture of a new vitamin "carbol" by ethynylation of an α,β unsaturated ketone has been illustrated by Wiederkehr [6]. As shown in Fig. 5, a cascade reaction column with multiple agitators was proposed to ensure good mixing of reactants during the required long mean residence time with a mini-

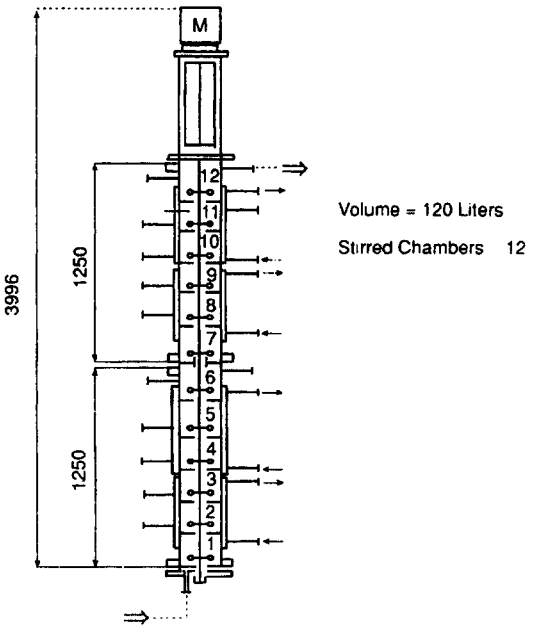


Fig. 5. A cascade reaction column with multiple agitators for the synthesis of vitamin "carbol" (after Wiedeskehr [6]).

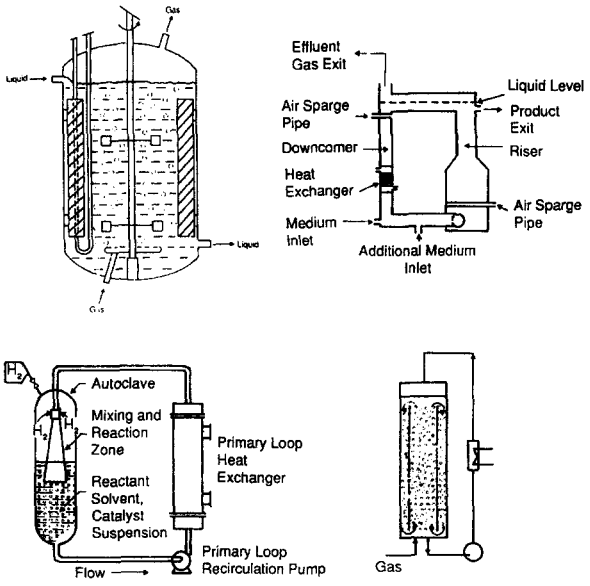


Fig. 6. Schematic of batch liquid catalytic reactors.

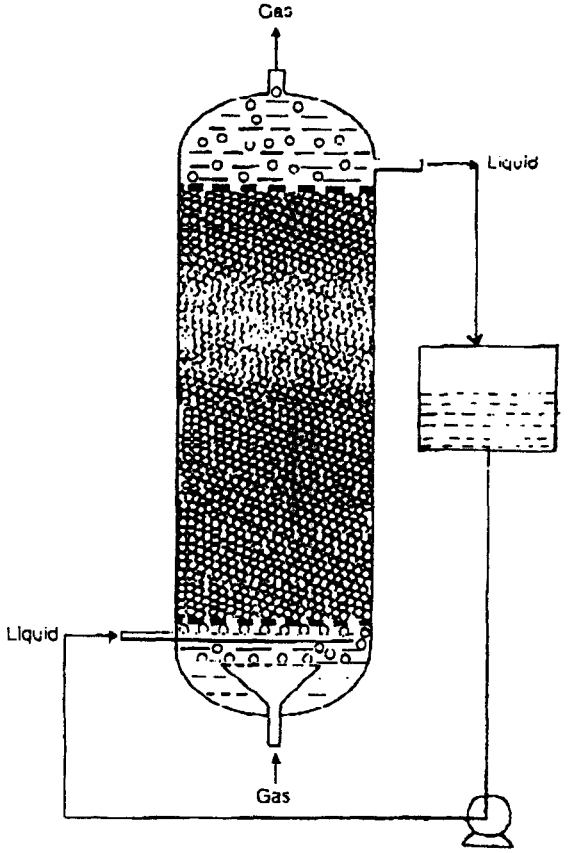


Fig. 7. Schematic of a fixed-bed semi-batch reactor with two-phase gas–liquid flow.

mum gas phase voidage. The latter was also required for safe operation, since acetylene was one of the reactants.

For gas–liquid and gas–liquid–solid reactions in pharmaceuticals processes, the commonly used reactor types are: (1) mechanically agitated reactors, (2) gas sparged or bubble column reactors and (3) jet loop reactors. Schematic diagrams for each reactor are shown in Fig. 6.

Fixed bed reactors with co-current upflow of gas and liquid, which are sometimes referred to as packed bubble column reactors, or downflow of gas and liquid corresponding to trickle bed reactors, are mainly used for large volume production of commodities and petrochemicals. However, as shown in Fig. 7, these reactors can also be used for batch or semi-batch operations in fine chemicals and pharmaceuticals with complete recycle of the liquid phase. With the development of shell-type supported metal catalysts, operation of fixed bed reactors with total recycle can provide better alternatives to mechanically agitated and bubble column reactors from the perspective of safety and catalyst handling.

For reactions with a large heat of reaction where the mass transfer limitations can be significant, the jet loop reactor is found to be most efficient due to its high heat and mass transfer efficiency. Many variations of these basic reactor types are practised in industry to achieve specific goals for a given process. Fig. 8 shows that novel reactors include multistage gas–liquid or slurry reactors, reactors with multiple agitators, monolithic catalytic reactors, air-lift and jet loop reactors, stirred tank reactors in series and cascade reaction columns. The type of agitators and cycle time, i.e., the required time to fill, heat, cool, vent and discharge, has been compared. The typical values of gas–liquid interfacial areas and overall heat transfer capability are given in Tables 5 and 6. The productivity was found to be highest for the Buss Loop reactor. The time required to execute non-productive steps in a batch cycle in this reactor was nearly one-half that required for conventional agitated and bubble column reactors. Other factors, such as catalyst attrition rates and reactor pressure, may

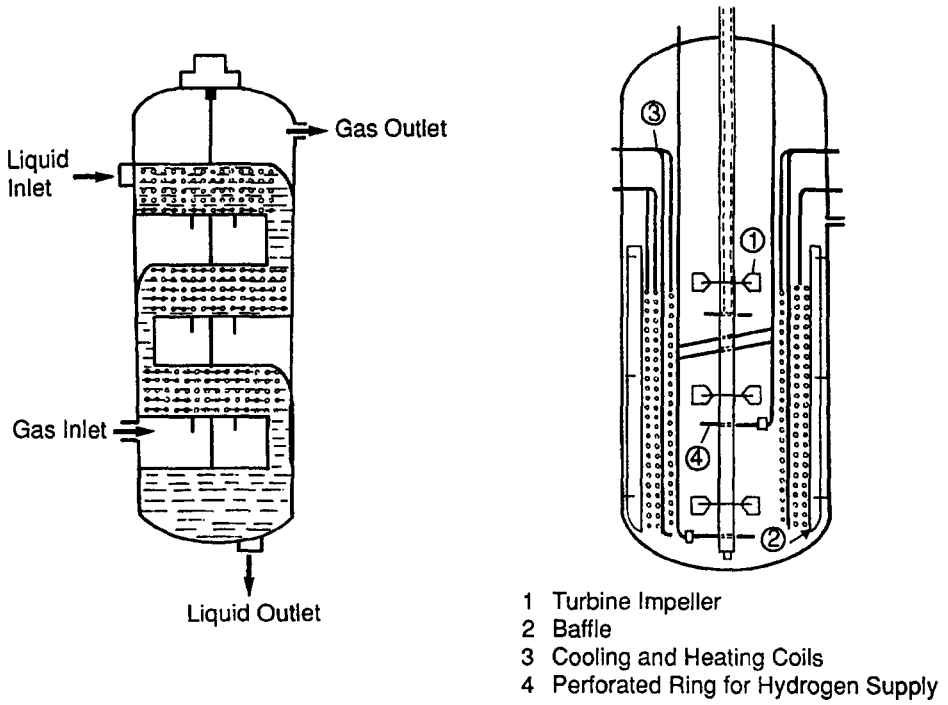


Fig. 8. Some examples of novel multiphase reactors: (a) Multistage trayed reactor; (b) Stirred reactor with multiple impellers and gas injection point.

Table 5
Gas/liquid interfacial characteristics of various reactor types (after Concordia [76])[a]

	Stirred tank reactor	Bubble column reactor	Buss™ loop reactor
Typical bubble diameter (mm)	3–6	4–8	1–2
Gas/liquid area (m^2/m^3)	1000–1500	600–1000	2000–3000
H_2 transfer rate (lb mol/gal/h)[a]	0.2	0.1	0.7

[a]1 lb=0.45 kg; 1 mol=0.024 m^3; 1 gal=3.79 l.

Table 6
Comparative heat transfer capability (after Concordia [76])

Reactor type	Heat transfer coefficient (Btu/h per ft^2 per °F)	Heat transfer capability (Btu/h per gal)
Stirred tank	80–90	2000–3000
Bubble column	40–50	1100–1700
Buss loop reactor	140–150	3000–8000

dictate the choice of another reactor type over the Buss Loop.

Common reactor types used for liquid–liquid and gas–liquid–liquid reactions are agitated reactors and conventional extracting equipment. Important considerations in the design of these include the effective liquid–liquid interfacial area and uniform dispersion of the appropriate liquid phase into a second liquid that serves as the continuous phase. The mode of operation of liquid–liquid and gas–liquid–liquid

reactors can be either batch, semi-batch or continuous feed of one or more reactants. Due to the smaller scales of operation, the type and number of agitators, heat exchanger area, baffles and spargers are often a key consideration.

The reactor types used for gas–liquid and gas–liquid–solid reactions are similar to those described above. An additional complication in the case of three phase slurry reactors is that uniform suspension of catalyst and handling of the slurry from the perspective of feeding, separation and recycle also must be considered in the reactor system design. For the classes of catalytic reactions that are most commonly encountered such as hydrogenation of organic compounds, gas-to-liquid mass transfer efficiency and temperature control are often important factors in the selection of a reactor type.

Concordia [76] has described the relative importance of the above key aspects for batch catalytic gas–liquid reactors. For the catalytic hydrogenation of dinitrobenzene, these authors have compared the performance of stirred tank (mechanically agitated), bubble column and Buss Loop reactors. For the same process, performance of these reactors was compared with respect to mass and heat transfer, interfacial areas, productivity and non-production time involving multi-purpose batch reactor systems. However, considering the various complexities in commercial processes for fine chemicals and pharmaceutical industries, along with the multiphase nature of these systems, semi-batch or continuous operation may be desirable in some cases.

For catalytic hydrogenation reactions and cases where single and pure gas phase reactant is involved, a dead-end or dead-headed type of batch reactor is sometimes used. Here, a continuous supply of the reactant gas is provided as dictated by the reaction demand so that no gas exits the system. This operation is also practicable for reactions involving two gases, such as hydroformylation or oxidative carbonylation, where feeding the gases in stoichiometric quantities is feasible or leads to safer operation. Since the apparent gas velocity in such reactors is limited to the consumption rate, additional devices, such as gas-induced agitation using hollow shafts, are necessary to achieve dispersion of gas bubbles in the liquid phase to achieve efficient gas-to-liquid mass transfer.

For reactions where gaseous products are formed, or a reactant gas is fed along with diluents, semi-batch reactors are preferred using gas feed rates that are much higher than the stoichiometric requirement. This has the net effect of stripping undesired volatile products from the liquid, or reducing the concentration of dissolved diluents in the liquid, which can reduce the net reaction rate. When several processes are operated in a typical pharmaceutical industry batch plant, continuous feed of liquid reactants over the batch time cycle is sometimes necessary to achieve the desired selectivity, product quality and to control the excess heat of reaction. Thus, various factors need to be considered in the optimum choice and design of reactors for these processes. This optimum is best identified by a robust reactor model whose operational parameters and configuration are solved in conjunction with optimization methods.

6. Overall rate of reaction

In order to understand the overall performance of multiphase reactors for processes in fine chemicals and pharmaceuticals, it is useful to develop mathematical models that allow prediction of the reactor performance in terms of conversion, selectivity and production rate. For most multiphase catalytic reactions, the reactor performance depends on the reaction kinetics, inter-particle and intra-particle mass transfer steps, mixing and flow patterns of the fluid and solid phases, and heat transfer characteristics. It is first necessary to evaluate the local rate of reaction in the presence of transport effects under differential conditions for each class of reaction. In this section, a theoretical analysis of the overall rate of reaction for the more common general categories of reactions, such as gas–liquid and gas–liquid–solid reactions, is presented. A qualitative description of the key factors affecting other complex systems, such as gas–liquid–liquid and gas–liquid–liquid–solid reactions, is also given.

In the analysis of overall rate of reaction, kinetic models for the intrinsic kinetics along with the influence of heat and mass transfer limitations must be considered. Therefore, the following sections present the current status of kinetic modeling, methods for determination of intrinsic kinetic rate parameters and

methods for prediction of mass transfer effects for gas–liquid and gas–liquid–solid catalytic reactions. Criteria for evaluating the degree of mass transfer limitations and the various regimes where the reaction is occurring are also discussed.

6.1. Intrinsic reaction kinetics

A knowledge of intrinsic reaction kinetics is the most essential element for analysis of reactor performance using first principles. Intrinsic kinetic data are specific to a particular catalytic reaction system, and are independent of the scale of operation. The general problem is to develop a rate equation that adequately represents the reaction kinetics over the range of commercial operating conditions. For this purpose, both empirical and mechanistic rate equations are used. In this section, the current status of kinetic modeling for gas-liquid catalyzed reactions will be presented.

6.1.1. Gas–liquid–solid catalyzed reactions

Gas-liquid-solid catalyzed reactions are most commonly used in processes for pharmaceuticals and fine chemicals wherein the reaction essentially occurs at the catalyst surface. To describe reaction mechanisms for these systems, classical Langmuir–Hinshelwood elementary steps are often used. The details of the kinetic modeling of gas–solid catalyzed reactions are described in detail by Froment and Bischoff [77] so these are omitted here. For reactions involving dissolved gas and liquid phase reactants and products, complexities such as competitive adsorption of the components, solvent effects and ionic media, and changes in the solubility of reacting gas in the liquid phase should be considered.

Some examples of kinetic rate equation models for gas–liquid–solid catalytic reactions that are relevant to fine chemicals and pharmaceuticals are summarized in Table 7. Most of these involve complex non-linear rate equations. In several cases, the reactants and products are very complex organic molecules with liquid–solid adsorption characteristics that are also non-linear, which affects the rate of reaction. The type and concentration of the solvent and impurities often has a notable effect on the intrinsic reaction rate. These features cannot be adequately described by Langmuir–Hinshelwood models, since these models are based on the assumption that one of the steps in the catalytic cycle is rate determining. However, in many applications, more than one elementary step can be rate limiting. Development of a kinetic model that accounts for these effects, in addition to those mentioned above, is a significant challenge.

One of the common methods used by chemists for discrimination between rate models is based on analysis of initial rate data. While this approach is useful to obtain a preliminary understanding of the kinetic trends with respect to operating parameters, it often fails to explain some important features related to product inhibition and changes in catalyst activity and selectivity with time-on-stream. Therefore, it is suggested that kinetic models should be verified for their applicability using both differential and integral analysis over a wide range of operating conditions, reactant conversions and product selectivities. An alternative approach involves discrimination between various models by direct application of the integral method of analysis. Several examples of this approach have been successfully demonstrated in the literature for gas–liquid–solid catalytic reactions [17,28,83].

Many processes involve complex multistep gas–liquid–solid catalytic reactions, wherein understanding of the intrinsic kinetics of each step becomes important for optimization of the selectivity to the desired product. Some examples include: (1) hydrogenation of 2,4-dinitrotoluene to toluene diamine [80]; (2) hydrogenation of adiponitrile to hexamethylene diamine [23,84]; and (3) hydrogenation of *p*-isobutyl acetophenone to *p*-isobutyl phenyl ethanol [81]. The important aspects of kinetic modeling for multistep reactions include: (1) the initial rate approach is not applicable, since it only explains the behavior of only the first reaction; (2) integral batch reactor data need to be analyzed that consider the entire reaction scheme vs. a limited set of reactions; (3) changes in the solubility of the reaction gas or gas mixture with the liquid-phase concentration often need to be considered; (4) independent experimental studies of the different steps to develop rate equations can be misleading and incorrect since the impact of competitive adsorption is not incorporated; (5) in some cases, pretreatment of the catalyst with the reactants, intermediates, or products changes the catalytic activity and nature of active sites; and (6) the model predictions should be validated using experimental data that spans

Table 7
Kinetic models for gas–liquid–solid catalytic reactions

Reaction system	Catalyst	Kinetic model	Reference
1. Hydrogenation of glucose	Raney-Ni	$\frac{wk_{11}AB}{(1+K_AA)}$	[12]
2. Ethynylation of formaldehyde to butynediol	Cu_2C_2–silical gel	$\frac{wk_{01}B}{(1+K_BB+K_EE)}$	[29]
3. Hydrogenation of *o*-nitroanisole	Pd/C	$\frac{wkAB}{(1+K_AA)(1+K_BB)}$	[16]
4. Oxidative carbonylation of aniline	Pd–C/NaI	$\frac{wkAEB^2}{(1+K_AA+K_BB+K_EE)^2}$	[78]
5. Hydrodesulfurization of *o*-aminobenzyl sulfides	$Co_xMo_yO_z$	$\frac{wk(P_{gA}/H_A)B}{(1+\sqrt{K_AP_{gA}/H_A})^2(1+K_BB)}$	[28]
6. Hydrogenation of 2-ethylhexenal	Pd–SiO_2-monolithic	$\frac{wkAB}{(1+\sqrt{K_AA}+K_BB+K_pP)^3}$	[79]
7. Hydrogenation of *m*-nitrochlorobenzene	Pt–S/C	$\frac{wkAB}{(1+K_BB)}$	[58]
8. Hydrogenation of 2,4-dinitrotoluene	Pd/Al_2O_3	$r_i = \frac{kK_HK_i(P_H/RT)^{0.5}C_i}{[1+K_H(P_H/RT)^{0.5}]\left[1+K_iC_i+\sum_{jj}K_jC_j\right]}$	[80]
9. Hydrogenation of *p*-isobutyl acetophenone	Ni/Y-Zeolite	$r_i = \frac{wk_iAC_i}{(1+K_AA)}$	[81]
10. Hydrogenation of 12-ethyl-5,6,7,8-tetrahydroanthraquinone	Pd/Support	$r_i = \frac{wkAB}{(1+\sqrt{K_AA})^2}$	[82]
11. Hydrogenation of 1,5,9-cyclododecatriene	Pd/Al_2O_3	$r_i = \frac{wk_iK_jA^nC_j}{\left(1+\sum_{j=1}^{3}K_jC_j\right)}$	[25]

a wide range of reaction conditions and conversion where the concentration profiles for each species can be compared.

A detailed case study of complex multistep catalytic reaction involved in hydrogenation of adiponitrile has been presented by Mathieu et al. [23] and Joly-Vuillemin et al. [84]. The stoichiometric reaction scheme considered for this commercially important reaction, which occurs in the manufacture of Nylon 6,6, was:

$$\underset{\text{Adiponitrile}}{NC-(CH_2)_4-CN} + 2H_2 \rightarrow \underset{\text{Aminocapronitrile(ACN)}}{NH_2-(CH_2)_5-CN} \quad (6.1a)$$

$$NH_2-(CH_2)_5-CN + 2H_2 \rightarrow \underset{\text{Hexamethylenediamine(HMD)}}{NH_2-(CH_2)_6-NH_2} \quad (6.1b)$$

Analysis of the experimental data lead to the following form of the rate equation.

In Eq. (6.2), C_H denotes the concentration of dissolved hydrogen, C_{ADN} is the concentration of adiponitrile and C_{ACN} is the concentration of aminocapronitrile. In this case, a reaction mechanism based on the reaction between dissociatively adsorbed hydrogen and adsorbed nitrile was considered as the rate-limiting step. However, the complex solvent effect was not quantitatively described by this L–H type of model.

Another example of kinetic modeling that has been investigated in detail is the hydrogenation of 2,4-dinitrotoluene using both Pd-on-carbon and Pd-on-Al_2O_3 type of catalysts [80,85]. For this case, two types of mechanisms have been considered. Molga and Westerterp [80] assumed a reaction between dissociatively adsorbed hydrogen and adsorbed organic compounds at different active sites for a Pd-on-Al_2O_3 catalyst where only the outer shell of the particle was coated with palladium metal. Nikaljee [85] proposed a rate model where the elementary step between adsorbed hydrogen and the liquid phase reactants

$$r_i = \frac{k_iK_iC_i\sqrt{K_HC_H}}{(1+\sqrt{K_HC_H}+K_{ADN}C_{ADN}+K_{ADN}C_{ADN}+K_{ACN}C_{ACN})^2}. \quad (6.2)$$

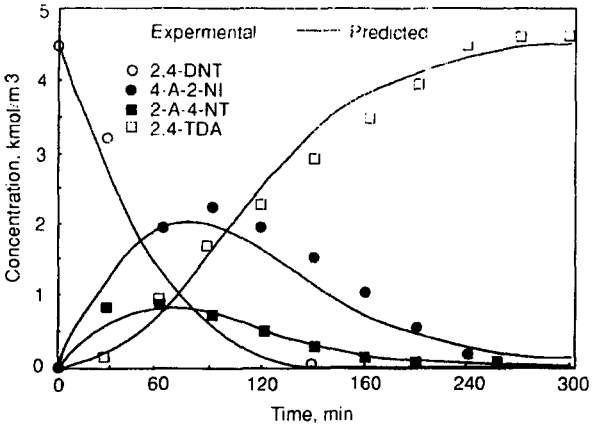


Fig. 9. Concentration versus time responses for hydrogenation of 2,4- dinitrotoluene in a slurry reactor at 323 K (after Nikaljee [85]).

was rate limiting. Typical concentration vs. time responses showing a comparison between experimental data and model predictions are shown in Fig. 9.

Rajshekharam and Chaudhari [81] have recently reported a detailed analysis of the intrinsic kinetics for the hydrogenation of *p*-isobutyl acetophenone using a Ni/Y zeolite catalyst in a slurry reactor. The reaction scheme is shown in Fig. 10. In addition to the formation of *p*-isobutyl phenyl ethanol, which is the desired product, other reactions leading to a variety of by-products are also significant. They proposed the following intrinsic rate equations for the steps shown in Fig. 10:

$$r_1 = \frac{wk_1 A^* B_L}{1 + K_A A^*}, \tag{6.3a}$$

$$r_2 = \frac{wk_2 A^* C_L}{1 + K_A A^*}, \tag{6.3b}$$

$$r_3 = wk_3 C_L, \tag{6.3c}$$

$$r_4 = \frac{wk_4 A^* E_L}{1 + K_A A^*}. \tag{6.3d}$$

Here, A^* denotes the equilibrium solubility of dissolved hydrogen, while the remaining symbols are defined in Fig. 10. A typical comparison between the experimental concentration-time data and the model predictions is shown in Fig. 11. This particular case represents negligible adsorption of the liquid phase components and the reaction between adsorbed hydrogen and liquid phase reactants is the rate-limiting step. One of the reaction steps involving formation of an ether derivative is a homogeneous reaction.

A recent trend in kinetic modeling involves a molecular level approach for the development of rate models. Evidence suggests that there is a close analogy between reaction mechanisms based upon adsorption and those based on molecular species through organometallic intermediate species. This aspect can allow better understanding of the kinetic trends in complex reactions, which are otherwise modeled using empirical approaches. A recent review on this subject is by Waugh [86], although examples of the molecular level approach for industrially important reactions involved in pharmaceuticals and fine chemicals are rare. This approach needs an independent study on the nature of catalytic sites and molecular species formed as intermediates. This might lead to a reaction scheme that can form the basis for deriving rate equations.

6.1.2. Gas–liquid homogeneous catalyzed reactions

Kinetic modeling of gas–liquid reactions catalyzed by homogeneous organometallic species has been mainly studied from the perspective of reaction mechanisms. Hence, only a few examples exist where detailed reaction rate models have been proposed that could be reliably used for reactor design purposes. Also, it is important to note that gas–liquid reactions have been traditionally analyzed for the purpose of designing gas-absorption systems. In the present context, only investigations that are relevant to gas–liquid reactor design involving homogeneous catalytic processes will be considered.

It is well-known in gas–liquid reactions with organometallic complexes that the reaction generally occurs between a dissolved gas or gases and the liquid phase reactants to produce a liquid and possibly gas phase products or volatile liquid products. In this class of reactions, it is often possible to describe the reaction mechanism through a series of stoichiometric reactions involving molecular species. Hence, the resulting catalytic cycle forms the basis for development of a kinetic model. Some examples of kinetic models for gasp–liquid catalytic reactions are given in Table 8. Many of these processes involve complex chemistry for which the reaction mechanism is not well understood and in such cases, empirical rate equations are used. To reiterate

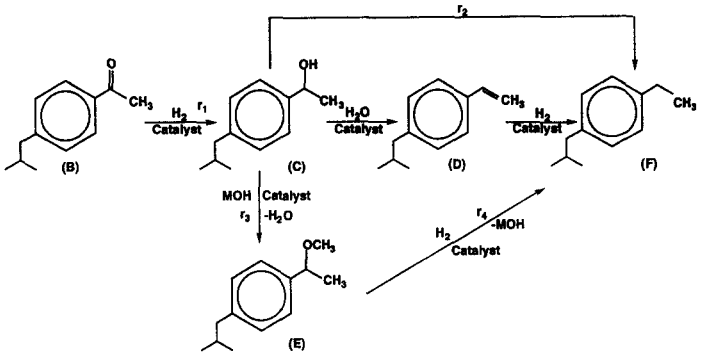


Fig. 10. Reaction scheme for hydrogenation of *p*-isobutyl acetophenone using a Ni/Y zeolite catalyst (after Rajashekharam and Chaudhari [81]): B=*p*-isobutylacetophenone; C=*p*-isobutylphenylethanol; D=*p*-isobutylvinylbenzene; E=*p*-isobutyl phenyl ethyl methyl ether; F=*p*-isobutylethylbenzene.

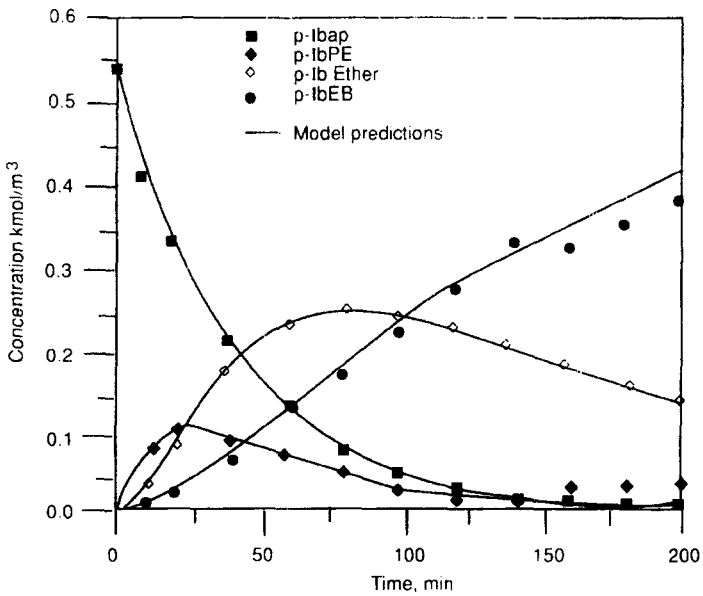


Fig. 11. Concentration vs. time responses for hydrogenation of *p*-isobutylacetophenone using a Ni/Y zeolite catalyst at 413 K (after Rajashekharam and Chaudhari [81]).

the point made earlier, a careful study of the concentrations of various reaction components, nature of solvent, solution pH and catalyst activity vs. time-on-stream, to name a few, must be made in the evaluation of rate models. A few illustrative examples of kinetic modeling in this category are discussed below.

Hydroformylation of 1-hexene and allyl alcohol has been studied by Deshpande and Chaudhari [91,92,93] using $HRh(CO)(PPh_3)_3$ catalyst. They proposed the following form of the rate equation:

$$r_A = \frac{k(A^*)^m B_L C_L E_L}{(1 + K_E E_L)^n (1 + K_B B_L)^p}. \quad (6.4)$$

The important features of this reaction are: (1) strong rate inhibition with an increase in the concentration of dissolved CO; (2) mild substrate inhibition with olefin; and (3) an increase in the

Table 8
Kinetic models used in gas–liquid-homogeneous catalyzed systems (after Mills et al. [2])

Reaction system	Catalyst	Rate equation	Reference
Hydrogenation of cyclohexene	$RhCl(PPh_3)_3$	$\frac{kABC}{1+K_AA+K_BB}$	[87]
Hydrogenation of alkyl alcohol	$RhCl(PPh_3)_3$	$\frac{kABC}{1+K_A+K_AK_BR^2}$	[88]
Hydroformylation of propylene	$HCo(CO)_4$	$\frac{kABC}{E}$	[89]
Hydroformylation of di-isobutylene	$Co_2(CO)_8$	$\frac{kABC}{E+K_AA}$	[90]
Hydroformylation of 1-hexene, alkyl alcohol and vinyl acetate	$HRhCO(PPh_3)_3$	$\frac{kA^mBCE}{(1+K_BE)^x(1+K_BB)^y}$	[91,92,93]
Oxidation of cyclohexane	$Mn(OAc)_2$	$\frac{kBC}{k_1+k_2C}$	[94]
Carbonylation of methanol	$RhCl_3^*HI$ solution	kCP	[95]
Carbonylation of ethanol	$RhCl_3^*HI$ solution	$kA^{0.8}B^{0.8}C^{0.66}$	[54]
Carbonylation of nitrobenzene	$Pd(py)_3Cl_3$	kAC	[96]

C: Concentration of carbon monoxide; P: concentration of the promoter HI.

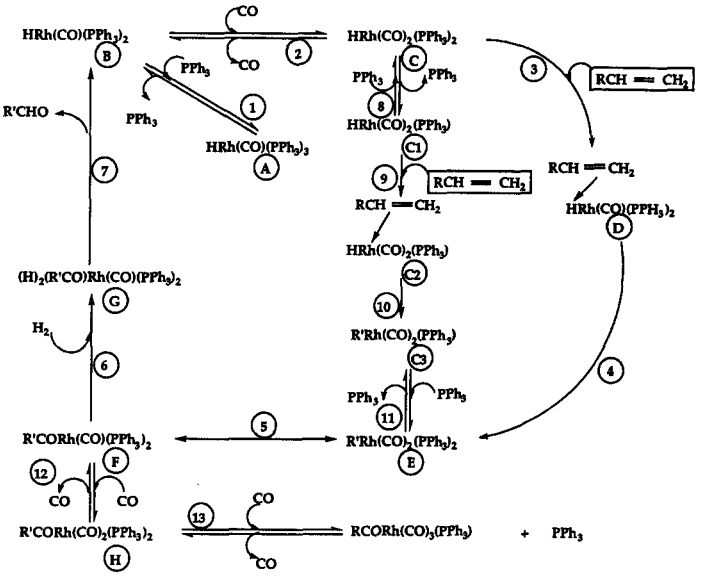


Fig. 12. Catalytic cycle for hydroformylation of olefins using a rhodium complex catalyst (after Evans et al. [97]).

rate with the concentration of dissolved H_2 and catalyst concentrations. Although, the catalytic cycle for hydroformylation is well-understood and the kinetic trends are consistent with the mechanism, the above rate equation is still only an empirical model.

Recently, Divekar et al. [56] have demonstrated a molecular level approach to kinetic modeling for the hydroformylation of 1-decene using rhodium complex catalyst. The hydroformylation mechanism considered is shown in Fig. 12. The rate equation was derived assuming that step (6) was rate controlling:

$$r_A = \frac{k' K_1 K_2 A^* B^* C_L D_L}{1 + K_2 B^* + K_1 K_2 B^* D_L + K_1 K_2 K_3 (B^*)^2 D_L + K_1 K_2 K_3 K_4 (B^*)^3 D_L}. \quad (6.5)$$

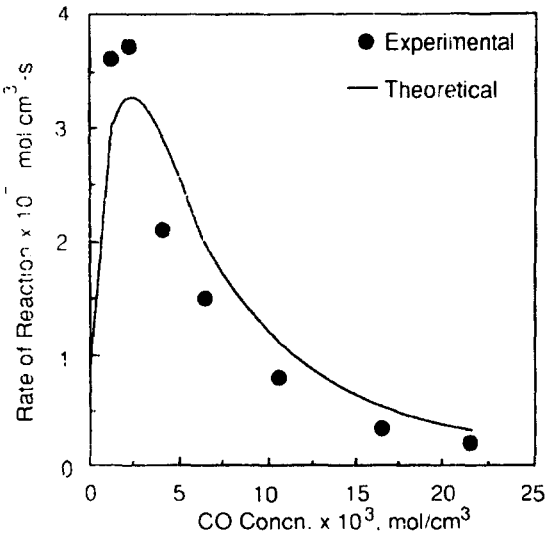


Fig. 13. Effect of CO concentration on the rate of hydroformylation of 1-decene using a rhodium complex catalyst (after Divekar et al. [56]).

This model predicts the negative order dependence with CO as shown in Fig. 13 for the hydroformylation of 1-decene to undecanal, which is a perfumery chemical.

Kinetic modeling for the multistep oxidation of *p*-xylene to terephthalic acid using a homogeneous cobalt organometallic catalyst has been studied by Cao et al. [98]. The reaction mechanism involves a complex series of steps so that a lumped reaction scheme involving key intermediates and final products has been proposed along with a semi-batch reactor model.

Although the above-cited work has increased knowledge on modeling of reaction kinetics for gas–liquid systems with soluble catalysts, further work in this area is clearly necessary until the results can be safely used for multiphase reactor analysis and design.

7. Mass transfer effects

Multiphase catalytic reactions are often practised in industry under conditions such that significant mass transfer limitations are present. Therefore, analysis of the overall rate of reaction under differential conditions is an important first step that must be followed before developing an integral reactor design model. In this section, a general outline of the overall rate expressions for gas–liquid and gas–liquid–solid catalytic reaction is presented. A detailed review of this area would be prohibitively lengthy and is beyond the scope of this paper. The interested reader may refer to the monographs by Danckwerts [99], Doraiswamy and Sharma [3] and Ramachandran and Chaudhari [4] for further details.

7.1. Gas–liquid reactions

The analysis of mass transport effects of gas–liquid catalytic reactions that occur in fine chemicals and pharmaceuticals has been studied for a very few cases, though the general principles are similar to that for non-catalytic reactions. The important steps are: (1) gas-to-liquid mass transfer and (2) reaction of the dissolved gaseous reactants with the liquid phase reactants either in the bulk liquid, at the gas–liquid interface, or some location in between, such as in the liquid film adjacent to the gas–liquid interface. The overall rate expressions for reaction for bimolecular, $m-n$ order and series–parallel reactions are given by Danckwerts [99], Astarita [100] and Doraiswamy and Sharma [3]. In this section, an overview of rate equations that are relevant to homogeneous catalytic reactions is given.

For homogeneous catalytic hydrogenation reactions, the intrinsic kinetics can often be represented by the following reaction rate equation:

$$r_A = \frac{kA^* B_L C_L}{1 + K_A A_L + K_B B_L}. \tag{7.1}$$

The analysis of mass transfer for this complex rate form is reported by Chaudhari [101]. For reactions that are confined to the bulk liquid, the overall rate of reaction in the liquid based upon the volume of the liquid phase is given by

$$R_A = k_L a(A^* - A_L) = \frac{kA_L B_L C_L}{1 + K_A A_L + K_B B_L}, \tag{7.2}$$

where A^* is the concentration of the dissolved gas. After rearranging this equation, the following form is obtained for the enhancement factor

E_A:

Another important example is the hydroformylation

$$E_A = \frac{R_A}{k_L a A^*} = \frac{(1 + k_a + k_b + H_{AO}^2\gamma) - \sqrt{(1 + k_a + k_b H_{AO}^2\gamma)^2 - 4k_a H_{AO}^2\gamma}}{2k_a}, \tag{7.3}$$

where $k_a = k_A A^*$, $k_b = K_B B_L$, $\gamma = k_L/D_A a$, and $H_{AO} = \sqrt{D_A k B_L C_L}/k_L$.

This equation is applicable for $H_{AO} \leq 0.8$.

For the fast reaction regime, where the reaction in the liquid film is significant, the following expression for the enhancement factor E_A has been derived [101]

$$E_A = \frac{H_A}{\tanh H_A}, \tag{7.4}$$

where

$$H_A = H_{AO}\left[\frac{2b_l}{k_a^2}\left\{k_a + (1+k_b b_i)\ln\frac{(1+k_b b_i)}{(1+k_a+k_b b_i)}\right\}\right]^{\frac{1}{2}}. \tag{7.5}$$

The overall rate for this case is given by

$$R_A = k_L a A^* E_A. \tag{7.6}$$

This model is applicable for $H_{AO} > 1$. A plot of E_A vs. H_{AO} is shown in Fig. 14.

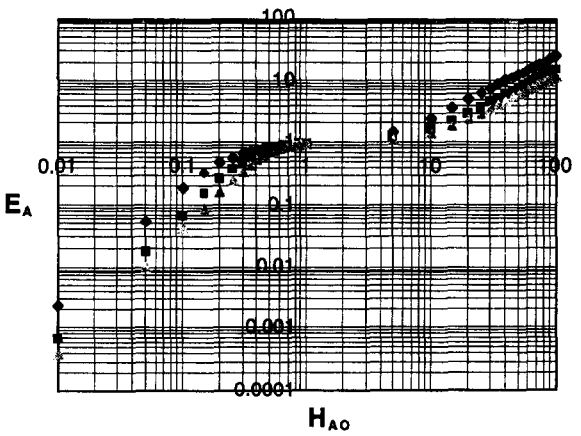


Fig. 14. Enhancement factor for E_A versus H_{AO} for gas–liquid homogeneous catalytic hydrogenation (After Chaudhari [101]): (◆, k_A=0.1; ■, k_A=5.0; ▲, k_A=10.0), Parameters – k_b=1.0, γ= 50.0, b_i=0.5, b_l=0.1.

of olefins in which simultaneous absorption of H_2 and CO is followed by a complex catalytic reaction with liquid reactant. This is a case of a negative order reaction with CO and first order with H_2 where the intrinsic kinetics are given by

$$r_A = \frac{kA^*B^*C_{cat}}{(1 + K_{A_2}B^*)^2}. \tag{7.7}$$

In Eq. (7.7), A^* denotes dissolved H_2, B^* denotes dissolved CO and C_{cat} is the concentration of the catalyst precursor. A detailed analysis of mass transfer for this case was given by Chaudhari [102]. It was shown that under conditions of significant mass transfer limitations, a combined result of a reaction with first order and negative order reaction with gas phase reactants (H_2 and CO) leads to trends that contradict commonly accepted general rules. For example, in spite of mass transfer limitations, the rate of reaction shows no significant impact of agitation speed for the specific case of hydroformylation of 1-hexene.

Homogeneous catalytic oxidation reactions often involve a redox type reaction mechanism in which re-oxidation of a catalytic species is an important step. For safety reasons, it is required to control and optimize the inlet oxygen concentration in a given gas–liquid reactor. Thus, a critical oxygen concentration exists to achieve steady state conversion of organic reactants for a given set of conditions. Bhattacharya and Chaudhari [103] have derived rate equations for critical O_2 concentration considering the olefin oxidation reaction that occurs in the Wacker process using a semi-batch bubble column reactor. The combined effects of gas–liquid mass transfer, reactant and catalyst concentrations, and mixing parameters were analyzed.

In summary, there are only a few rare studies on the detailed kinetics of gas–liquid catalytic reactions. Hence, a need exists to investigate reaction engineering aspects of homogeneous catalytic reactions under

commercially relevant conditions. An important example that deserves special attention is the asymmetric hydrogenation in the manufacture of L-dopa using homogeneous catalysis. In this case, the reaction occurs between dissolved H_2 and dissolved solid reactant to produce an insoluble as well as a soluble product. Here, simultaneous dissolution of a gas and solid reactant followed by a catalytic reaction needs to be considered along with precipitation of a product. A need also exists for detailed case studies on such important reactions, which includes experimental verification of rate models.

7.2. Gas–liquid–solid reactions

The analysis of the overall rate of reaction for three-phase gas–liquid–solid catalytic reactions is now well-developed where the effects of various mass transfer steps are included. A detailed account of this subject is given by Ramachandran and Chaudhari [4]. In this section, the general outline for a bimolecular reaction A(g)+νB(l)→P(l) that occurs in a porous catalyst and related rate models are given, which can be extended to other specific cases.

The analysis for non-porous catalysts, i.e., catalysts where the active layer is deposited on an impervious support, is not included. However, the approach is similar, except diffusion and reaction does not occur. Instead, gas–liquid and liquid–solid mass transfer occur in series with the surface catalyzed reaction. The latter can be defined in terms of the catalytic surface area, which can be determined by various surface characterization techniques. As shown in Fig. 14, the important steps involved in a gas–liquid–solid catalytic reaction that occurs in a porous catalyst include:

- Transport of the gas phase reactant A from gas phase to the bulk liquid.
- Transport of A and liquid reactant B from the bulk liquid to the catalyst surface.
- Intraparticle diffusion of A and B in the pores of the catalyst.
- Adsorption of A and B on the catalyst surface followed by a chemical reaction to yield the products.

For these multiphase catalytic reactions, it is convenient to express the observed rate of reaction in terms of an overall effectiveness factor η_0 defined as

$$\eta_0 = \frac{R_A}{wk(A^*)^m B_L^n}. \tag{7.8}$$

For a $m-n$ order reaction, the overall effectiveness factor η_0 is given as

$$\eta_0 = \frac{[1-(\eta_0/\sigma_A)]}{\phi_o}\left[\coth\left\{3\phi_o\left(1-\frac{\eta_0}{\sigma_A}\right)^{(m-1)/2}\right\} - \frac{1}{3\phi_o(1-(\eta_0/\sigma_A))^{(m-1)/2}}\right], \tag{7.9}$$

where σ_A and ϕ_o are defined as

$$\sigma_A = \frac{A^*\left[\frac{1}{k_L a}+\frac{1}{k_s a_p}\right]^{-1}}{wk(A^*)^m B_L^n} \tag{7.10}$$

and

$$\phi_0 = \frac{R}{3}\left[\frac{(m+1)S_p k(A^*)^{m-1}B_L^n}{2D_e}\right]^{1/2}. \tag{7.11}$$

The overall rate of reaction is then given as

$$R_A = \eta w k(A^*)^m B_L^n. \tag{7.12}$$

For other cases involving more complex L–H type kinetics, such as the reaction between two dissolved gases and non-isothermal effects, the works of Ramachandran and Chaudhari [4] and Merchan et al. [104] are suggested.

7.3. Gas–liquid–liquid reactions

Reactions involving biphasic catalysis and phase transfer agents have the distinguishing characteristic that two immiscible liquid phases are involved. Since many new applications of this technique are emerging for synthesis of pharmaceuticals and fine chemicals, a detailed analysis of the overall rate of reaction is needed. Reaction engineering aspects and overall rate analysis for biphasic hydroformylation of olefins are briefly discussed by Chaudhari et al. [74]. For analysis of the overall rate of a gas–liquid–liquid reaction, two cases must be considered: (1) when the aqueous phase holdup is lower than the organic phase holdup, the aqueous phase droplets are dispersed in the continuous organic phase with dispersed gas bubbles and (2) when the organic phase holdup is smaller than the aqueous

phase holdup, organic droplets are dispersed in the continuous aqueous phase with dispersed gas bubbles. These two models will result in different expressions for overall rates depending on the type of catalyst and solvent used, phase equilibrium properties and magnitudes of the gas–liquid and liquid–liquid mass transfer resistances. The droplet size of the dispersed phase and its distribution are dependent on properties of the liquid medium, reactor type and details of the internal reactor design. The average droplet size is also dependent on coalescence and breakage behavior of the system, particularly in the presence of electrolytes and surfactants.

For phase transfer catalytic reactions, such as the carbonylation of benzyl chloride to phenyl acetic acid, the catalytic cycle involves reactions in both phases with or without liquid–liquid mass transfer limitations. In the analysis of the overall rate of reaction for such cases, a dynamic analysis is necessary to evaluate the concentrations of various intermediate species, since more than one reaction, and possibly mass transfer steps, could be rate limiting. There is a need to do further research in this area, including considering the complexities of changes in the hydrodynamics and mass transfer behavior due to two immiscible liquid phases. The overall rate of reaction in gas–liquid–liquid reactions as encountered in phase transfer catalysis would depend on the following parameters: (1) intrinsic kinetics of the reaction steps; (2) solubility of gases in two liquid phases; (3) gas–liquid and liquid–liquid mass transfer coefficients; (4) drop size of the dispersed phase and (5) liquid–liquid equilibrium properties for the reactants and products.

8. Controlling regimes and criteria for mass transfer analysis

In order to set forth an appropriate model for multiphase catalytic reactors, it is necessary to analyze the significance of controlling regimes. This is also necessary when conducting kinetic experiments and when performing the subsequent kinetic data analysis to ensure that the resulting kinetic parameters correspond to the intrinsic kinetics regime. It is more practical to derive the criteria based on the initial rate of reaction, since this is usually the condition that gives the maximum rate for the reactant. The controlling regimes are discussed below for gas–liquid and gas–liquid–solid catalytic reactions, since these are the most common class of multiphase reactions encountered in practice.

8.1. Gas–liquid catalyzed reactions

Gas–liquid reactions take place in different regimes depending on the relative rates of mass transfer and chemical reaction for a given set of reaction conditions. Typical concentration profiles for a bimolecular reaction between a gas phase and a liquid phase reactant are shown in Fig. 15. These regimes of reactions can be broadly classified into two categories: (1) reaction occurring in the bulk liquid (H_A<1.0) and (2) reaction occurring in the gas–liquid film (H_A>>1.0). Fortunately, many homogeneously catalyzed reactions for most commercial processes fall into the first category, since the rates are relatively slow compared to the rate of gas–liquid mass transfer. The criteria for the controlling regimes are given below where E_A is the enhancement factor:

Kinetic control:

$$E_A = \frac{R_A}{k_L a A^*} < 0.1. \tag{8.1}$$

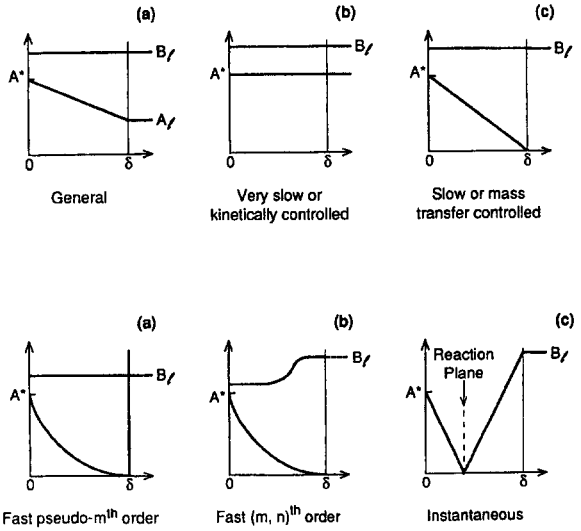


Fig. 15. Concentration profiles and controlling regimes for a gas–liquid reaction.

Diffusion control:

$$E_A = \frac{R_A}{k_L a A^*} \approx 1. \tag{8.2}$$

Fast reaction regime with significant reaction in the liquid film:

$$\frac{B_{LO}}{\nu A^*} \gg E_A > 0.1. \tag{8.3}$$

Instantaneous reaction regime:

$$E_A \approx \left(1 + \frac{B_{LO}}{\nu A^*}\right). \tag{8.4}$$

Use of these criteria requires an experimentally measured point value for the rate, the solubility of the gas phase reactant and an estimate of gas-to-liquid mass transfer coefficient, $k_L a$.

8.2. *Gas–liquid–solid catalyzed reactions*

In three-phase gas–liquid–solid catalyzed reactions, it is important to assess the significance of gas–liquid, liquid–solid and intraparticle mass transfer resistances. The criteria used for these are:

Gas–liquid mass transfer:

$$\alpha_{gl} = \left[\frac{R_A}{k_L a A^*}\right] < 0.1. \tag{8.5}$$

Liquid–solid mass transfer:

$$\alpha_{ls} = \left[\frac{R_A}{k_s a_p A^*}\right] < 0.1, \tag{8.6}$$

where

$$a_p = 6w/\rho_p d_p. \tag{8.7}$$

Intraparticle diffusion:

$$\phi_{exp} = \frac{d_p}{6}\left[\frac{\rho_p R_A}{w D_e A^*}\right]^{0.5} < 0.2, \tag{8.8}$$

where

$$D_e = \frac{D\epsilon_p}{\tau}$$

In applications where the concentrations of liquid reactants vary significantly during a process, it is also important to check if significant concentration gradients exist within the catalyst particle. Details of these are discussed by Ramachandran and Chaudhari [4]. For example, for a bimolecular reaction, the following criteria must be satisfied to assume that only the dissolved gaseous reactant is limiting:

$$\frac{D_{eB} B_s}{\nu D_{eA} A_s} > 10. \tag{8.9}$$

A typical concentration profile is shown in Fig. 16. However, these are only a few illustrations for a particular case and more detailed analysis will be necessary for systems involving complex series-parallel consecutive reactions and highly exothermic reactions where temperature gradients can become significant.

For reactions with two immiscible liquid phases, it is necessary to evaluate the significance of liquid–liquid mass transfer limitations in addition to gas–liquid mass transfer. The following criteria for absence of liquid–liquid mass transfer limitation can be estimated using the following inequality:

$$\alpha_{LL} = \frac{R_A}{k_{LL} a_L} < 0.1, \tag{8.10}$$

where $aL = 6\epsilon_{ld}/d_0$, ϵ_{ld} is the dispersed phase holdup and d_0 is the average drop size.

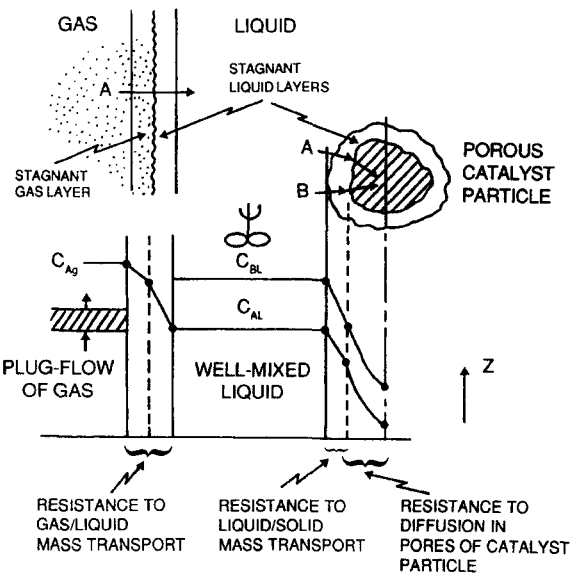


Fig. 16. Concentration profiles for a gas–liquid–solid catalytic reactions.

9. Basic reactor models

Reactor models are required to predict and to analyze the performance of the various multiphase reactor types under integral conditions as a function of various design, kinetic and transport parameters. For multiphase catalytic processes as commonly encountered in the manufacture of pharmaceuticals and fine chemicals, batch and semi-batch operations are more commonly used because the production rates are small when compared to commodities and larger-scale fine chemical processes. In certain cases, continuous flow stirred reactors (CFSTR), bubble columns and fixed-bed reactors with multiphase flow are also used for specific cases. In this section, an outline of basic design models for batch/semi-batch gas–liquid and gas–liquid–solid reactors is provided. For additional details, one may refer the monographs by Danckwerts [99], Doraiswamy and Sharma [3], and Ramachandran and Chaudhari [4].

9.1. Gas–liquid reactors

For semi-batch gas–liquid catalytic reactors, which may include mechanically agitated or bubble column reactors with or without liquid recycle, the simplest case of practical interest is an isothermal reaction with non-volatile liquid reactants and products where the gas phase consists of a single component. For a bimolecular reaction with the stoichiometry. A(g)+νB(l)→ Products, the governing material balance equation for the liquid reactant B_l is given by

$$-\epsilon_l \frac{dB_L}{dt} = \nu R_A = \nu k_L a A^* E_A, \tag{9.1}$$

where R_A is the rate of reaction per unit volume of dispersion, ϵ_l is the liquid holdup and E_A is the reaction enhancement factor. Expressions for E_A for selected cases were summarized in Section 7.1. For gas–liquid reactions of this type, the regimes of absorption are likely to change over a batch time so that the appropriate expressions for E_A must be used. Integration of Eq. (9.1) yields the following expression for the batch time t_B

$$t_B = \frac{\epsilon_l}{\nu k_L a} \int_{B_{Lf}}^{B_{Li}} \frac{dB_L}{A^* E_A(B_L)}. \tag{9.2}$$

Changes in A^* as a function of B_L or product concentrations should also be incorporated. The enhancement factor E_A is a function of Hatta number, H_{A0}, which for a bimolecular reaction is defined as $H_{A0} = \sqrt{D_A k_l B_l}/k_L$. Thus, E_A is a function of B_l and its dependence would vary for different reaction kinetics and regimes of reaction. The above integral can be easily evaluated by numerical quadrature to evaluate the batch time of reaction for a specified conversion level. For non-isothermal reactions, the variation of the suspension temperature with time should be considered. Some details of non-isothermal reactor modeling are summarized in the review of Mills et al. [2].

9.2. Gas–liquid–solid reactors

Semi-batch three-phase gas–liquid–solid catalyzed reactors are commonly used for hydrogenation, oxidation and alkylation reactions. In these systems, the gas phase flows continuously through the reactor with no inflow or outflow of the liquid phase. Analogous to gas–liquid reactors, the concentrations of the reacting species vary as a function of time. Hence, the relative contribution of mass transfer and reaction resistances changes, and this must be accounted to properly estimate the batch time. Ramachandran and Chaudhari [4] have described semi-batch reactor models for different cases. The equations for evaluation of batch time assuming (1,0) and (1,1) order kinetics and a bimolecular reaction A(g)+νB(l)→Products are given below:

(1,0) order reaction

$$t_B = \frac{B_{Li} X_B}{\nu A^*} \left[\frac{1}{k_L a} + \frac{1}{k_s a_p} + \frac{1}{\eta_c w k_l} \right], \tag{9.3}$$

where

$$\eta_c = \frac{1}{\phi} \left[\coth(3\phi) - \frac{1}{3\phi} \right] \tag{9.4}$$

and

$$\phi = \frac{R}{3} \left[\frac{\rho_p k_l}{D_e} \right]^{1/2}. \tag{9.5}$$

(1,1) order reaction

$$t_B = \frac{B_{Li} X_B}{\nu A^*} \left[\frac{1}{k_L a} + \frac{1}{k_s a_p} \right] + \frac{B_{Li} R^2 \rho_p I}{3 A^* w D_e}, \tag{9.6}$$

where

$$I = \frac{2}{\phi_i^2} \times \ln\left[\frac{\phi_i \cosh\phi_i - \sinh\phi_i}{\phi_i\sqrt{1-X_B}\cosh(\phi_i\sqrt{1-X_B}) - \sinh(\phi_i\sqrt{1-X_B})}\right] \quad (9.7)$$

and

$$\phi_i = R\left[\frac{\rho_p k_2 B_{Li}}{D_e}\right]^{1/2}. \quad (9.8)$$

This model can be used to predict the reaction batch time in the presence of gas–liquid, liquid–solid and intraparticle diffusion transport resistances.

In many practical examples, various complexities, such as non-linear kinetics, solubility changes with concentrations and non-isothermal effects, are present. In such cases, the batch reactor model must be solved numerically. Rode and Chaudhari [83] have illustrated the modeling of a semi-batch slurry reactor for the hydrogenation of *p*-nitrochlorobenzene, which represents an example of a complex non-linear kinetics with a highly exothermic reaction. More recently, Rajashekharam and Chaudhari [105] have demonstrated the use of semi-batch reactor models for a complex multistep reaction scheme. The hydrogenation of 2,4-dinitrotoluene in a semi-batch slurry reactor provides another interesting example of a complex reaction with large heat effects. The modeling of a continuous stirred tank reactor for this system was investigated by Molga and Westerterp [80] and Janssen et al. [106], which also incorporated the effect of an evaporating solvent. The experimental verification of a semi-batch non-isothermal reactor for hydrogenation of 2,4-dinitrotoluene was also recently reported by Rajashekharam et al. [105]. Typical results are shown in Fig. 17.

The details of continuous reactor models are given by Ramachandran and Chaudhari [4]. The methodology described therein can be used to develop models for specific examples of interest in pharmaceutical industry. In recent years, jet loop reactors are used for many processes in fine chemicals and pharmaceuticals. As described earlier, this reactor type has a distinguishing characteristic of very efficient gas-to-liquid mass transfer and heat transfer. The modeling of a jet loop reactor is, therefore, of practical interest.

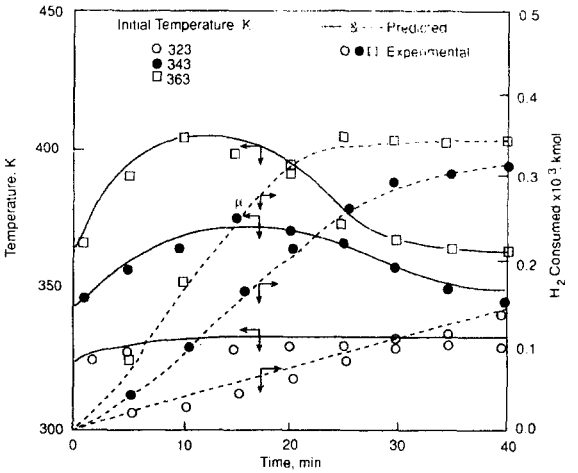


Fig. 17. Consumption of hydrogen gas and ΔT_{max} vs. time at different reaction temperatures. Reaction conditions: Concentration of DNT=0.46 kmol/m^3; Catalyst concentration=1.25 kg/m^3; Solvent=EtOAc; Hydrogen pressure=1.38 MPa; Agitator speed=18 Hz; Reaction volume=1.25x10^{-4} m^3 (after Rajashekharam et al. [105]).

This reactor operation differs from the conventional agitated reactors with respect to the following aspects:

1. In agitated reactors, the liquid phase is completely backmixed and the rate is considered to be uniform throughout the dispersed phase volume. In jet loop reactors, the reaction contribution can be different in the jet nozzle, the bulk liquid holding tank and the remaining reactor volume used for the recycle stream and heat exchanger.
2. The controlling reaction regime and mass transfer coefficients may be different in each reaction zone in a jet loop reactor. The same comment applies to the mass transfer coefficients, in contrast to mechanically agitated reactors.

The above discussion suggests that it is necessary to first analyze the extent of reaction occurring in each zone. It is believed that the jet nozzle region is mainly effective in saturating the liquid stream with the gas phase reactant due to very high mass coefficients even though the residence time is very short. The major reaction takes place in the bulk liquid vessel between the pre-dissolved gas and liquid phase reactants. However, no significant reports are available in the literature in which quantitative analysis of the jet loop

reactor is given. Even in the bulk liquid vessel, complete backmixing may not be a realistic assumption. Further work in this area with experimental verification is necessary.

10. Correlations for mass transfer parameters

As shown earlier in Section 6, the evaluation of overall local reaction rates and reactor performance requires a knowledge of the reaction intrinsic kinetics and the mass transfer parameters. In this section, key correlations for gas–liquid, liquid–solid, liquid–liquid and intraparticle mass transfer parameters are given for some commonly used reactors.

10.1. Mechanically agitated reactors

Various correlations for the volumetric gas–liquid mass transfer coefficient k_La in mechanically agitated reactors have been proposed by several investigators. These have been compared by Ramachandran and Chaudhari [4] for the same set of operating conditions and thermodynamic transport parameters. General reviews on this subject are published by Joshi et al. [107] and Beenackers and van Swaaij [108] to which the reader is referred for details.

A popular correlation for k_La is the one proposed by Yagi and Yoshida [109].

$$\frac{k_La d_I^2}{D} = 0.06\left(\frac{d_I^2 N \rho_L}{\mu_L}\right)^{1.5}\left(\frac{d_I N^2}{g}\right)^{0.19}\left(\frac{\mu_L}{\rho_L D}\right)^{0.5} \times \left(\frac{\mu_L u_g}{\sigma_L}\right)^{0.6}\left(\frac{N d_I}{u_g}\right)^{0.32}. \quad (10.1)$$

Bern et al. [110] have proposed the following correlation for k_La using catalytic hydrogenation data under mass transfer limited conditions in pilot-scale reactors with a capacity of 30 and 500 litres.

$$k_La = 0.326 N^{1.16} d_I^{1.98} u_g^{0.32} V_L^{-0.52} \quad (10.2)$$

In slurry reactors with a catalyst loading less than 10% (w/v), the k_La values are relatively unaffected by the presence of solid particles. However, for higher catalyst loading, a decrease in k_La is observed. The predictions of correlations vary widely and differences of ±30% for a unified correlation can be expected for a given set of parameters. These differences are probably due to variations in the internal design details of the reactors, the system thermodynamic and transport properties and measurement errors. Pharmaceuticals and fine chemical processes contain liquids whose transport properties are notably different from those of water due to the presence of polar, non-polar and in some cases, viscous organic compounds. It is well-known that the transport and related properties have a strong influence on the bubble coalescence and hence the bubble diameter, gas-to-liquid interfacial area and k_L values [111]. Generally, polar solvents and electrolytic solutions lead to higher k_La values due to smaller bubble size as the coalescence process is suppressed for these systems as a result of electrostatic double layer repulsion forces. No quantitative description of the coalescence effect has been incorporated in the k_La correlations so far and more work on this aspect of mass transfer would be useful.

The liquid-to-solid mass transfer coefficient k_s in a mechanically agitated reactor can be estimated using a correlation proposed by Sano et al. [112]:

$$\frac{k_s d_p}{DF_c} = 2 + 0.4\left(\frac{e d_p^4 \rho_L^3}{\mu_L^3}\right)^{1/4}\left(\frac{\mu_L}{\rho_L D}\right)^{1/3}. \quad (10.3)$$

Here, F_c is the shape factor of the particles, e is the energy supplied per unit mass of the slurry and the liquid–solid contact area is $a_p = 6w/\rho_p d_p$. An example of evaluating (10.3) is given by Ramachandran and Chaudhari [4].

The liquid-to-liquid mass transfer coefficient k_{LL} in agitated reactors can be calculated using the following correlations proposed by Calderbank [113].

Dispersed droplets to continuous phase:

$$k_{LL} = 0.42\left(\frac{\Delta\rho\mu_{LC} g}{\rho_{LC}}\right)^{1/3}\left(\frac{\mu_{LC}}{\rho_{LC} D}\right)^{1/2}. \quad (10.4)$$

Continuous phase to dispersed droplets:

$$k_{LL} = 0.13\left(\frac{P\mu_{LC}}{\nu_d \rho_{LC}^2}\right)^{1/4}\left(\frac{\mu_{LC}}{\rho_{LC} D}\right)^{-2/3}. \quad (10.5)$$

The liquid–liquid interfacial area a_{LL} can be calculated by the following expression:

$$a_L = \frac{6\epsilon_{ld}}{d_0}, \tag{10.6}$$

where ϵ_{ld} is the dispersed phase holdup and d_0 is the average drop size of the dispersed droplets. The drop size distribution and d_0 would depend on the agitation intensity, location of stirrer and physical properties of the two liquid phases. The value of d_0 can be estimated from the following correlation proposed by Okufi et al. [114] based on data for different tank sizes, stirrer speeds and dispersed phase holdups:

$$\frac{d_o}{d_I} = 0.126(1 + 2\epsilon_{ld})We^{-0.6}\left(\frac{d_I}{D_{ref}}\right)^{-0.4}, \tag{10.7}$$

where d_I is the impeller diameter and *We* is the Weber number.

10.2. Bubble column reactors

The key correlations for gas–liquid and liquid–solid mass transfer coefficients in a bubble column reactor are given below:

Hikita et al. [115] correlation for k_La:

$$k_La = \frac{14.9gf}{u_g}\left(\frac{u_g\mu_L}{\sigma_L}\right)^{1.76}\left(\frac{\mu_L^4 g}{\rho_L\sigma_L^3}\right)^{-0.284} \times \left(\frac{\mu_g}{\mu_L}\right)^{0.243}\left(\frac{\mu_L}{\rho_L D}\right)^{-0.604}. \tag{10.8}$$

Kobayashi and Saito [116] correlation for k_s:

$$\frac{k_s d_p}{D} = 2 + 0.212\left[\frac{d_p^3(\rho_p - \rho_L)g}{\mu_L D}\right]^{1/3}\left[\frac{d_p u_g \rho_L}{\mu_L}\right]^{0.112}. \tag{10.9}$$

In Eq. (10.8), f=1.0 for non-electrolytes, such as water, butanol, methanol and sugar solutions. For electrolyte solutions, correlations for f are given in terms of the ion concentration. The mass transfer characteristics, and particularly k_La, are strongly dependent on the transport properties. For example, for electrolytic solutions and aqueous organic solutions containing a surfactant, the coalescence of gas bubbles is suppressed. This phenomena results in a smaller average bubble diameter and hence larger specific interfacial area. These aspects have not been incorporated in the correlation proposed earlier and need further study. The basic features of coalescence of gas bubbles in gas–liquid dispersions have been recently reviewed by Chaudhari and Hofmann [111].

10.3. Jet loop reactors

The values of k_L and a for a jet loop reactor were measured by Blenke and Hirner [117]. The values of k_L are not very strongly dependent on fluid dynamics in highly turbulent systems like a jet loop reactor. Over a wide range of gas velocity (u_g=0.4–6.5 cm/s), the average k_L value was 4.6×10^{-2} cm/s. The interfacial area can be calculated by the following correlation which is expressed in terms of the power input *P*.

$$a = 5.4 \times 10^3 u_g^{0.4}\left(\frac{P}{V_L}\right)^{0.66}. \tag{10.10}$$

For a typical case of highly turbulent flow and P/V_L of 2 kW/m^3, the approximate k_La value in a jet loop reactor is around 7 s^{-1}, which is significantly higher than that observed for agitated and bubble column reactors.

11. Summary and conclusions

Multiphase catalytic processes that occur in the manufacture of pharmaceuticals, fine chemicals and specialty chemicals have been reviewed along with key reaction engineering concepts for analysis of reactor performance in laboratory to commercial-scale applications. Particular attention was devoted to more recent applications where routes based on classical organic synthesis have been replaced with more efficient catalytic chemistries that utilize recent discoveries of novel soluble organometallic complexes and heterogeneous solids. Particular topics that were covered included: (1) selected applications that employ novel heterogeneous or homogeneous catalysts; (2) methods for classification of various reaction types that can be used as a preliminary guide to reactor selection and analysis; (3) distinguishing features of multiphase gas–liquid, gas–liquid–solid, liquid–solid, gas–liquid–liquid–solid and other related classes of reactions; (4) description of commonly used multi-

phase reactor types; (5) governing equations for evaluation of the overall reaction rate in the presence of transport effects, including selected examples of intrinsic kinetic rate models; (6) two-film theory models for assessment of mass transfer effects in gas–liquid, gas–liquid–solid and gas–liquid–liquid reactions, along with methods for identification of the controlling regimes; (7) models for batch and semi-batch reactors and (8) correlations for evaluation of commonly used mass transport coefficients. In each of the above categories, an attempt was made to identify particular features and complicating aspects that were relevant to applications in pharmaceuticals, fine chemicals and specialty chemicals.

In Sections 2, 3, 4, an abbreviated review was given on selected multiphase reactions that have commercial relevance in the manufacture of pharmaceuticals and fine chemicals. The synthesis of novel heterogeneous catalyst compositions, such as zeolites, supported noble metals, heteropolyacids and metal oxides, has provided more opportunities for devising direct routes for adding or modifying functionality to molecules having various degrees of complexity. Similarly, sophisticated organometallic complexes are being discovered that allow precise control of chemoselectivity, regio-selectivity and stereoselectivity. This is particularly relevant in pharmaceuticals where a particular optical isomer has the desired medicinal activity. Design of homogeneous catalyst systems that exhibit the required activity and selectivity and that can be readily separated has received increased emphasis. Isolation of the desired product from the reaction mixture and catalyst recovery are key issues. The use of computational chemistry to guide the design of catalysts for multiphase systems is in an early stage of development, but has potential as an enabling technology.

A brief review of multiphase reactor types that are commonly used to execute pharmaceutical and fine chemical reactions in pilot and commercial-scale equipment was given in Section 5. The particular ones discussed included mechanically agitated reactors, bubble column reactors and jet loop reactors. These are attractive reactor types for applications where a single reactor system must manufacture various products, since they have process flexibility. The choice of one reactor type over another for long-term manufacture of a given product should be made using a combination of process modeling, experiments, optimization and process economics. Hence, a case-by-case analysis is often necessary before the final choice of a reactor type can be made.

The final four sections reviewed models for prediction of the local rate of reaction in the presence of transport effects, methods for identification of the controlling reaction regime criteria for assessing the magnitude of transport effects, basic design equations for batch and semi-batch reactors and selected correlations for estimation of mass transfer coefficients. Experimental data to support the development of improved correlations for design and scale-up that apply to commercial systems are clearly lacking. For this reason, scale-up, of new processes should proceed with caution, and rely upon a combination of reactor model development with experimental verification using laboratory and pilot-scale data as the basis. A critical aspect of this effort should include a comprehensive program on determination of intrinsic reaction kinetics, since this forms the basis for reactor modeling. For troubleshooting, optimization and retrofitting of existing reactors, the same information is needed to analyze reactor performance.

Although it was not included in the review, a knowledge of flow patterns for the various phases that participate in the reaction is also necessary for reactor model development. Modern experimental methods that allow measurement of tracer responses and hydrodynamical parameters of the reaction medium, such as bubble size distribution, local voidages, liquid velocity and recirculation are now available and should be used to guide reactor model development. These also are useful tools for diagnosing reactor performance, and can provide a basis for improving and optimizing reactor operation.

12. Notation

a	gas–liquid interfacial area per unit volume of reactor, m^2/m^3
a_L	liquid–liquid interfacial area per unit volume of reactor, m^2/m^3
a_p	external area of particles per unit volume of reactor, m^2/m^3
A^*	concentration of dissolved gaseous A in the liquid, $kmol/m^3$

A_L concentration of species A in the bulk liquid, kmol/m^3

A_s concentration of species A at the catalyst surface, kmol/m^3

b_i concentration of species B at the interface, dimensionless

b_l concentration of species B in the bulk liquid, B_L/B_{Li}, dimensionless

B^* concentration of dissolved gaseous B in the liquid, kmol/m^3

B_L molar concentration of species B in bulk liquid, kmol/m^3

B_{Lf} final concentration of species B, kmol/m^3

B_{Li} initial concentration of species B, kmol/m^3

B_{LO} concentration of species B in the bulk appearing in Eq. (8.3), kmol/m^3

C_{ACN} concentration of aminocapronitrile, kmol/m^3

C_{ADN} concentration of adiponitrile, kmol/m^3

C_H concentration of dissolved hydrogen gas, kmol/m^3

C_i concentration of species i, kmol/m^3

C_L concentration of species C in the liquid, kmol/m^3

d_I impeller diameter, m

d_0 average liquid drop size, m

d_p average particle diameter, m

D molecular diffusion coefficient, m^2/s

D_A molecular diffusion coefficient of species A, m^2/s

D_B molecular diffusion coefficient of species B, m^2/s

D_e effective diffusion coefficient in the catalyst pores, m^2/s

D_{eA} effective diffusion coefficient of species A, m^2/s

D_{eB} effective diffusion coefficient of species B, m^2/s

D_L concentration of species D in the liquid, kmol/m^3

E_A enhancement factor for gas–liquid reactions, dimensionless

E_L concentration of species E in the liquid, kmol/m^3

F_c shape factor of the particles appearing in Eq. (10.3), dimensionless

g acceleration due to gravity, m^2/s

H_A Hatta number appearing in Eq. (7.5), dimensionless

H_{AO} Hatta number appearing in Eq. (7.3), dimensionless

I function defined by Eq. (9.7), dimensionless

k intrinsic rate constant, kmol/m^3 s

k_1 first order rate constant appearing in Eq. (6.3a), m^3/kg s

k_2 first order rate constant appearing in Eq. (6.3b), m^3/kg s

k_3 first order rate constant appearing in Eq. (6.3c), m^3/kg s

k_4 first order rate constant appearing in Eq. (6.3d), m^3/kg s

k_a adsorption equilibrium constant, $K_A A^*$, dimensionless

k_b adsorption equilibrium constant, $K_B B_L$, dimensionless

k_i intrinsic rate constant appearing in Eq. (6.2), kmol/kg s

k_L gas–liquid mass transfer coefficient, m/s

k_{LL} liquid–liquid mass transfer coefficient, m/s

k_s liquid–solid mass transfer coefficient, m/s

K_{ACN} adsorption equilibrium constant for aminocapronitrile, m^3/kmol

K_{ADN} adsorption equilibrium constant for adiponitrile, m^3/kmol

K_A adsorption equilibrium constant for species A, m^3/kmol

K_B adsorption equilibrium constant for species B, m^3/kmol

K_E adsorption equilibrium constant for species E, m^3/kmol

K_H adsorption equilibrium constant for dissolved hydrogen, m^3/kmol

K_i adsorption equilibrium constant for species i, m^3/kmol

L height of the reactor, m

m order of reaction

n order of reaction

N speed of agitation in a mechanically agitated reactor, rev/s

p order of reaction

P power consumption for agitation of the liquid, W

r_A intrinsic rate reaction of species A, kmol/m^3 s

r_i intrinsic rate of reaction, kmol/kg s

r_1 intrinsic rate of reaction of species 1 appearing in Eq. (6.3a), kmol/m^3 s

r_2 intrinsic rate of reaction of species 2 appearing in Eq. (6.3b), kmol/m^3 s
r_3 intrinsic rate of reaction of species 3 appearing in Eq. (6.3c), kmol/m^3 s
r_4 intrinsic rate of reaction of species 4 appearing in Eq. (6.3d), kmol/m^3 s
R catalyst radius, m
S_p particle geometric area ($4\pi R^2$ for a spherical pellet), m^2
t denotes time, s
t_B batch time required to achieve a specified conversion, s
u_g superficial gas velocity, m/s
V_L volume of the liquid in the reactor, m^3
w catalyst mass per unit volume of reactor, kg/m^3
We Weber number appearing in Eq. (10.6)
X_B conversion of species B

Greek symbols

α_{gl} gas–liquid mass transfer coefficient appearing in Eq. (8.5), dimensionless
α_{ls} liquid–solid mass transfer coefficient appearing in Eq. (8.6), dimensionless
α_{ll} liquid–liquid mass transfer coefficient, dimensionless
γ mass transfer coefficient, dimensionless
ϵ_l liquid holdup
ϵ_{ld} dispersed liquid phase holdup
ϵ_p particle porosity
η_c catalyst effectiveness factor for a first order reaction
η_0 overall effectiveness factor
μ_G gas viscosity, kg/m s
μ_L liquid viscosity, kg/m s
μ_{Lc} liquid viscosity in the continuous phase, kg/m s
υ stoichiometric coefficient of species B in the reaction
υ_d kinematic viscosity of dispersed phase, m^2/s
ρ_L liquid density, kg/m^3
ρ_{Lc} liquid density in the continuous phase, kg/m^3
ρ_p density of the catalyst particle, kg/m^3
σ_L surface tension of the liquid, N/m
τ tortuosity of the catalyst particle
σ_A parameter defined by Eq. (7.10), dimensionless
ϕ Thiele modulus defined by Eq. (9.4)
ϕ_0 generalized Thiele modulus defined by Eq. (7.11)

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