12

DESIGN OF DISTILLATION AND EXTRACTION OPERATIONS

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12.1 INTRODUCTION TO SEPARATION DESIGN BY DISTILLATION AND EXTRACTION

Distillation and extraction are two important but often neglected unit operations in pharmaceutical process design and scale-up. Other than filtration following crystallization, these two processes represent the primary means of separating the important products of a complex manufacturing recipe from unwanted by-products, solvents, and other wastes. Successful design and execution of distillation and extraction operations have a direct impact on the purity and efficiency of downstream processing. These unit operations are material and cycle time intensive—often representing the point of maximum dilution and longest processing times in a synthetic manufacturing step. The cumulative effect of numerous distillation and extraction systems in active pharmaceutical ingredient (API) manufacture can be a determining factor in work center productivity in terms of kilograms of product per cubic meter of vessel space per week of operation. Beyond direct productivity, the overdesign of either unit operation leads to impacts on inventory and waste treatment systems—from thermal incinerators to solvent recovery to wastewater treatment facilities. Significant capital investments are often required to transport, store, recover, or treat liquids separated from products. The decision to waste or recover these liquids will have a direct impact on common green chemistry metrics such as the E-factor, which is defined as kilograms of waste per kilogram of product. Therefore, it is vital for process development chemists and their chemical engineering counterparts to jointly design the most efficient use of time and materials outside of traditional interests of bond-forming chemistry and product isolation.

12.1.1 Phase Equilibrium Thermodynamics

12.1.1.1 Phase Rule Distillation and extraction design is based on the fundamentals of phase equilibrium thermodynamics. Two phases in equilibrium must exist at the same temperature, pressure, and each species distributed between phases must possess identical partial molar Gibbs free energies in each phase.

$$T_\alpha = T_\beta$$

$$P_\alpha = P_\beta$$

$$G_i(T_\alpha, P_\alpha) = G_i(T_\beta, P_\beta)$$

The Gibbs phase rule for nonreactive components states that the number of degrees of freedom or the number of intensive state variables, available to fully specify a closed system at equilibrium is

$$F = C + 2 - P$$

where C is the number of distinct components, and P is the number of phases in equilibrium. Intensive variables are those that are independent of the size of a system as opposed to extensive variables that are a function of size. Mass and volume are examples of extensive variables, while temperature, pressure, and mass or mole fractions are intensive.

Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing Edited by David J. am Ende

For example, a binary system in vapor–liquid equilibrium consists of two components and two phases in equilibrium, which results in two degrees of freedom ($F = 2 + 2 - 2 = 2$). Therefore, exactly two independent, intensive state variables (temperature, pressure, or mass/mole fraction of one species) may be specified to define the system at equilibrium.

12.1.1.2 Fugacity/Partial Fugacity

As shown previously, partial molar Gibbs free energies are equivalent at equilibrium. Partial molar Gibbs free energy is also known as the chemical potential, μ_i, in phase equilibrium thermodynamics; and therefore, the chemical potentials of each component in each phase are equivalent at system equilibrium. Since chemical potential cannot be directly quantified, it can be conveniently redefined as a pseudopressure known as fugacity by the relationship

$$f_i = C \exp\left(\frac{\mu_i}{RT}\right)$$

where C is a temperature-dependent constant [1]. Partial molar fugacities of each component in each phase are therefore equivalent at equilibrium.

$$f_{i\alpha} = f_{i\beta}$$

In the vapor phase under ideal gas conditions, partial molar fugacity is equal to partial pressure (p_i), or

$$p_i = \frac{P}{y_i}$$

where P is total pressure and y_i is the mole fraction of component i. For ideal gas conditions or systems in which molecular interactions are absent in the vapor phase, can be assumed at moderate temperatures and at pressure of less than 10 bar, which holds true of most systems in pharmaceutical processing. Activity is defined as the partial molar fugacity of a component relative to its fugacity at some standard state. If the standard state is chosen as the fugacity of the pure component at the same temperature and pressure, then activity is

$$a_i = f_i/f_0 \text{ or } f_i = a_i f_0$$

Partial molar activity, a_i, can be further defined as the product of an activity coefficient, γ_i, and the mole fraction of the component, or for the liquid phase

$$a_i = \gamma_i x_i$$

where x_i is the mole fraction of a component in the liquid phase. Combining terms, the partial molar fugacity of a component in the liquid phase is therefore

$$f_i = \gamma_i x_i f_0$$

The standard state fugacity for a pure component at a given temperature is known as the vapor pressure, or $P^*(T)$.

12.1.1.3 Raoult's Law

As stated previously, in vapor–liquid equilibrium the partial molar fugacities are equal, which forms the basis for Raoult's law for vapor–liquid equilibrium

$$f_{(i,v)} = f_{(i,l)} \text{ or } y_i P = \gamma_i x_i P_i^*(T)$$

For an ideal solution of components, the activity coefficient would be unity for all components across all possible compositions. Few multicomponent solutions exhibit ideal behavior upon mixing; and therefore, activity coefficient data are an essential part of phase equilibrium calculations. For noncondensable species with a mole fraction in solution approaching zero, Raoult's law can be restated by combining the activity coefficient and vapor pressure terms into what is known as a Henry's constant, H_i, and therefore Henry's law.

$$y_i P = x_i H_i$$

Liquid–liquid equilibrium follows the same thermodynamic principles; and therefore, equilibrium between phases can be described in a similar fashion and may include equilibrium with a vapor phase as well. That is, the partial molar fugacities of fugacities of each component of each phase must be equal, or

$$f_{i\alpha} = f_{i\beta} = f_{i\gamma}$$

where α is the vapor phase, β is the first liquid phase, and γ is the second liquid phase. Substituting know values for partial molar fugacities for each phase and assuming ideal gas behavior for the vapor phase, we have

$$y_i P = \gamma_{i\beta} x_{i\beta} P_i^*(T) = \gamma_{i\gamma} x_{i\gamma} P_i^*(T)$$

Since the pure component vapor pressure is independent of phase composition, this term can be eliminated from the equality to define vapor–liquid–liquid (VLL) equilibrium as

$$y_i P / P_i^*(T) = \gamma_{i\beta} x_{i\beta} = \gamma_{i\gamma} x_{i\gamma}$$

For noncondensable vapor, Henry's law for equilibrium between VLL phases would be

$$y_i P = H_{i\beta} x_{i\beta} = H_{i\gamma} x_{i\gamma}$$

12.1.1.4 Extended Antoine Equation

Pure component vapor pressure data is well correlated as a function of temperature by an empirical relation known as the Antoine equation. In its extended form, the Antoine equation is

$$\ln \mathrm{P}_i^*(T) = C_{1i} + \frac{C_{2i}}{(T + C_{3i})} + C_{4i}T + C_{5i}\ln(T) + C_{6i}T^{C_{7i}}$$

where $P_i^*(T)$ is vapor pressure of component i and T is temperature. Parameter values are widely available in online data banks and within commercial properties and process simulation packages such as Aspen Properties and Aspen Plus.

*12.1.1.5 **K-Values*** Phase equilibrium is also represented frequently by ratios known as K values. In vapor–liquid equilibrium, this is simply the ratio of vapor to liquid mole fractions of a single component.

$$K_i = \frac{y_i}{x_i}$$

In relation to Raoult's law, this equilibrium constant can be restated as

$$K_i = \gamma_i P_i^*(T)/P$$

In the liquid–liquid equilibrium case, the K value is a ratio of mole fractions in each liquid phase and is known as a distribution coefficient

$$K_{iD} = \frac{x_{i\alpha}}{x_{i\beta}}$$

or through the phase equilibrium definition for the liquid–liquid system

$$K_{iD} = \frac{\gamma_{i\alpha}}{\gamma_{i\beta}}$$

Ratios of vapor–liquid equilibrium constants for a pair of components, i and j, are known as relative volatility, α, while the ratio of liquid–liquid equilibrium constants for a pair of components, i and j, are referred to as relative selectivity, β

$$\alpha = \frac{K_i}{K_j} = \frac{\gamma_i P_i^*(T)}{\gamma_j P_j^*(T)}$$

$$\beta = \frac{K_{iD}}{K_{jD}} = \frac{\gamma_{i\beta}\gamma_{j\alpha}}{\gamma_{i\alpha}\gamma_{j\beta}}$$

These ratios provide an alternative means of describing equilibrium between components although they remain temperature and composition dependent. Further, the ratios often provide a basis of comparison when selecting components in separation design. For instance, relative volatility may be used to determine the value of constant-level distillation as a means of separating a pair of components. Also, relative selectivity is useful in evaluating liquid–liquid extraction systems, where the choice of solvent is important to for efficient enrichment of the extract phase in the solute without undesirable carryover of feed solvent to the same.

12.1.2 Process Design from Laboratory to Manufacturing Plant

Accurate and efficient design of equilibrium stage separations requires fundamental physical property data for individual components and binary pairings as well as computational tools to store properties in data banks, to predict phase equilibrium, and to design new equipment or specify the operation of an existing plant. The range of activities leading to process design begins with component screening, phase diagramming, and single-stage equilibrium modeling. Most often in pharmaceutical manufacturing operations, a process design must fit the constraints of existing plant equipment, which is usually limited to relatively simple vessels with heat transfer utilities for establishing phase equilibrium, and in the case of vapor–liquid equilibrium an overhead condenser to separate vapor as distillate from the equilibrium vessel. Distillate is typically collected in a similar type of vessel and this by-product is sometimes sent to a separate facility on site for solvent recovery through further distillation. Liquid–liquid extractions are performed in similar equipment except that the receiver is used to collect the lower phase once equilibrium is established at the desired temperature and sufficient time is allowed for phases to separate. The separated phases in their respective vessels are then further processed with additional extractions using fresh solvent to achieve the desired design end point. For the reasons outlined here, the focus of subsequent sections will be single-stage equilibrium and separation design, although many of the early stage activities detailed here are applicable to selection and evaluation of solvents for relative volatility and selectivity as a basis for comparison of systems.

12.2 DESIGN OF DISTILLATION OPERATIONS

12.2.1 Vapor–Liquid Equilibrium Modeling

The graphical presentation of vapor–liquid equilibrium requires a collection of vapor pressure and activity coefficient data to calculate the mole fraction of each component in each equilibrium phase. Primary data from the laboratory are preferred as a starting point, but another valuable source of data is that contained within well-recognized data banks such as those of NIST, DIPPR, and DETHERM. In the absence of laboratory or a data bank source, pure component and binary properties may be estimated with the aid of property evaluation tools such as COSMOthermX or Aspen Properties. These tools use quantum chemical calculation of screening charge density or functional group contribution methods to provide pure component and binary data estimates.

*12.2.1.1 **Pure Component Vapor Pressure Data*** Fugacity of the liquid phase in Raoult's law is the product of an activity coefficient, liquid mole fraction, and the pure component vapor pressure. Vapor pressure is a function of temperature, and the data is often stored in tabular form or regressed into parameters of the extended Antoine equation for convenience and for use in modeling software. Figure 12.1 shows a collection of vapor pressure data plotted in semilog fashion for a set of common solvents.

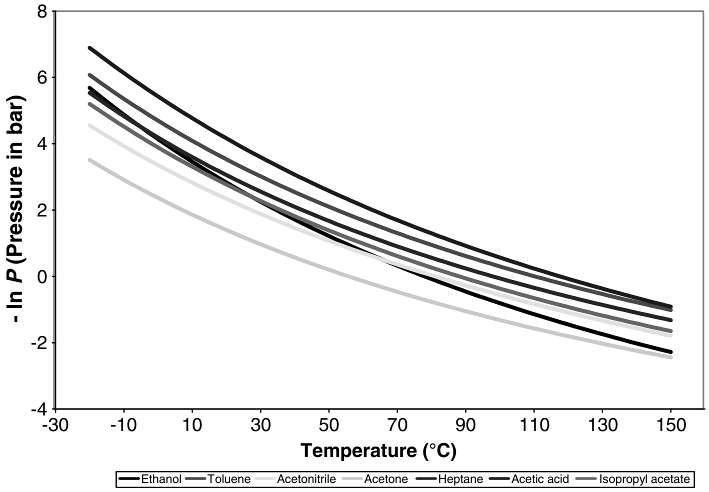


FIGURE 12.1 Vapor pressure of organic solvents.

12.2.1.2 Binary Activity Coefficient Data Activity coefficient data are vital to ensuring accurate nonideal solution vapor–liquid equilibrium modeling. Whether obtained from laboratory or estimated from equilibrium data, activity coefficients from binary pairs are typically regressed into NRTL binary interaction parameters, which may or may not be temperature dependent depending on the level of accuracy. The NRTL model is preferred for its ability to provide activity coefficient values for vapor–liquid and systems that display liquid–liquid immiscibility as well as predict maxima and minima in activity coefficients, where other models such as the Wilson equation are limited to vapor–liquid systems. The utility of this data is not limited to binary system, however, as the NRTL equation uses binary interaction parameters of possible parings of interest in a given system to calculate the liquid-phase activity coefficients for binary, ternary, and higher order systems. Figure 12.2 shows a set of binary activity coefficient plots for solvent pairs exhibiting a variety of behavior in solution. In ideal solutions, the activity coefficients of all components would be equal to unity. Strongly interacting solvents exhibit negative deviations from unity, while repulsive interactions are represented by positive deviations. In binary systems, the activity coefficient of a solvent is equal to unity at infinite dilution of all other components, which is shown in all plots at a mole fraction of unity.

12.2.1.3 Binary Phase Diagrams Simple binary phase diagrams contain a wealth of information about phase equilibrium behavior for a pair of solvents. Figure 12.3 shows examples of diagrams that combine vapor pressure and activity coefficient data of binary mixtures into a graphical representation of phase equilibrium for vapor–liquid and vapor–liquid–liquid systems. Generally, phase diagrams are divided into constant-pressure and constant-temperature plots. The constant-pressure phase equilibrium diagram, also known as a *T*-*xy* plot, is more common than the constant-temperature phase equilibrium diagram, or *P*-*xy* plot. The *T*-*xy* plot displays equilibrium temperature on the vertical axis versus liquid (x) and vapor (y) mole or mass fraction of one component on the horizontal axis. In a binary system, the mole or mass fraction of the other component in equilibrium is simply the difference between 1 and the plotted fraction. Several points of interest exist on either type of binary phase diagram including those that indicate the presence of an azeotrope or liquid–liquid immiscibility. On the left and right vertical axes, the liquid and vapor lines intersect at the boiling points of the pure components at the pressure or temperature specified by the plot. On a *P*-*xy* plot, these would be the pressure boiling points, while on a *T*-*xy* plot the pure component boiling point temperatures are indicated. Azeotropes are indicated by the intersection of the liquid and vapor curves between anywhere between 0 and 1 on the composition axis. In other words, vapor and liquid composition are equal at this point and are further defined by a temperature or pressure based on vertical position on the plot. On the *T*-*xy* plot, if this intersection occurs at a temperature less than the boiling temperature of either pure component (i.e., below the intersection of the liquid and vapor lines at either end of the composition axis), this is a minimum boiling azeotrope. If this temperature is greater than the boiling temperature of either pure component, this is a maximum boiling azeotrope. The reverse is true for less commonly used *P*-*xy* diagrams, since pressure is plotted on the vertical axis; that is, minimum boiling azeotropes appear above the boiling point pressures on either vertical axis. Azeotropes are divided into two classes heterogeneous and homogeneous. Homogeneous azeotropes are those that form in a single liquid phase, while heterogeneous azeotropes form in mixtures with liquid–liquid immiscibility. Further,

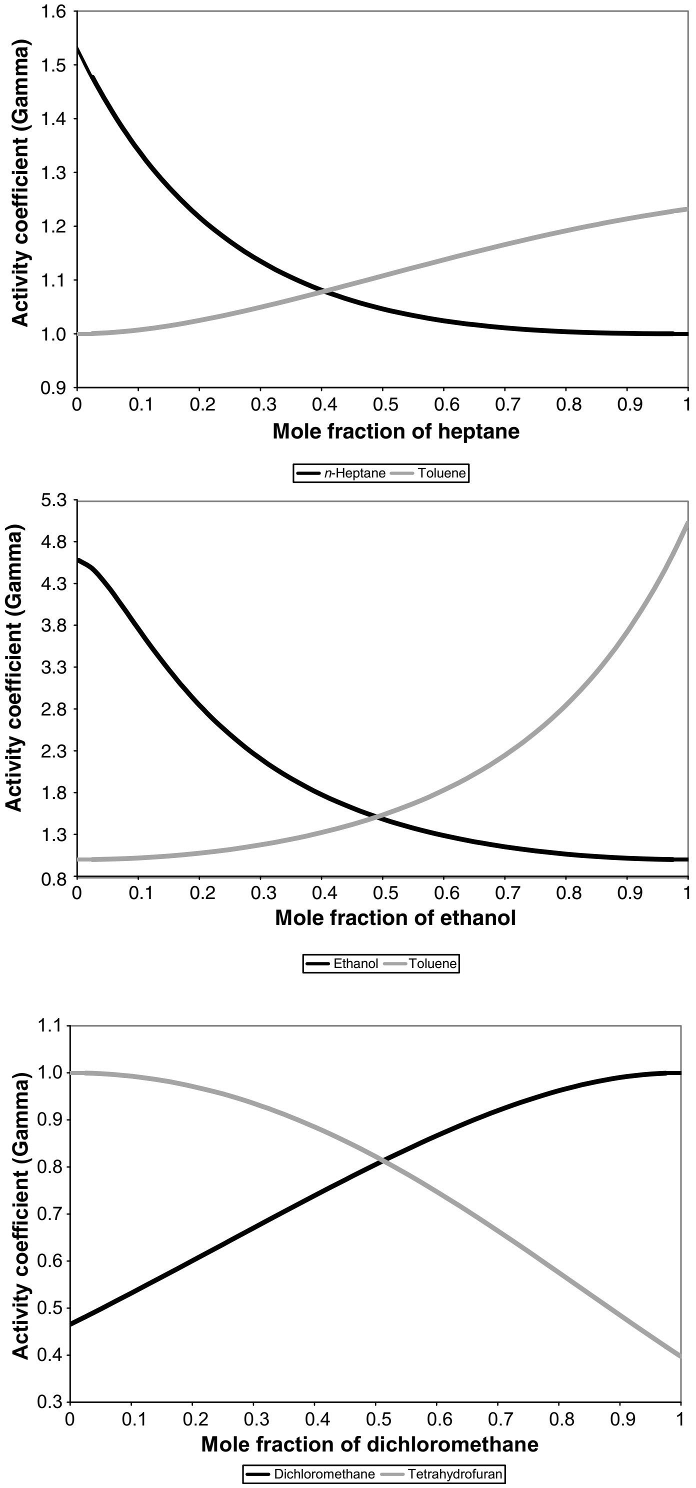


FIGURE 12.2 Liquid-phase activity coefficients as a function of composition.

heterogeneous azeotropes are always minimum boiling azeotropes, since a significant positive deviation in activity must occur for liquid-phase splitting to occur. On binary phase diagrams, liquid-phase immiscibility is indicated by a horizontal line for some portion of the composition range. A heterogeneous azeotrope occurs at the intersection of the vapor curve with this horizontal line. Heterogeneous liquid systems boil at a constant temperature indicated by the

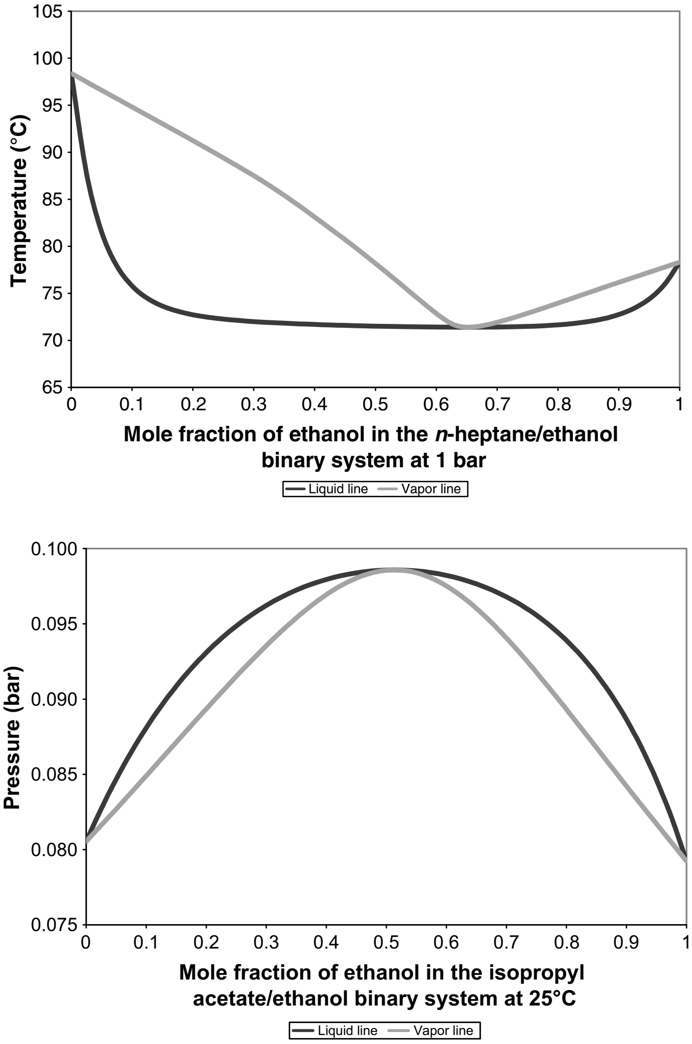


FIGURE 12.3 Vapor–liquid equilibrium-phase diagrams.

horizontal line position on the vertical axis of the *T*-*xy* plot. The composition of the liquid phases in equilibrium for these systems is indicated by the end points of the horizontal line. Constant temperature boiling continues until the system becomes homogeneous in the liquid phase, at which point the pot boiling point increases as the more volatile component is evaporated from the mixture.

EXAMPLE 12.1 DISTILLATION OF A *n*-HEPTANE AND ETHANOL BINARY MIXTURE

A 100 mole mixture of *n*-heptane (50 mol%) and ethanol (50 mol%) will be distilled to displace *n*-heptane from ethanol at ambient pressure. What is the initial boiling point of this mixture? As the mixture is distilled, which component will be enriched in the pot? If ethanol is not enriched in the pot, how much ethanol must be added to start at a composition that will distill to enrich the pot in ethanol? If sufficient ethanol is added to a point of 85 mol% ethanol, what is the initial boiling point of the mixture and what is the vapor composition in equilibrium at the start of distillation. What is the relative volatility at the initial mixture?

Solution

The *T*-*xy* phase diagram in Figure 12.3 shows that the initial boiling point of the mixture is about 72°C, and as the mixture boils the vapor composition is approximately that of the azeotrope (65 mol% ethanol, 35 mol% *n*-heptane), which will enrich the pot in *n*-heptane as the boiling point increases to that of 98°C. To begin at a point that will enrich the pot in ethanol, additional ethanol must be added to achieve a composition beyond the minimum-boiling azeotrope. To reach an initial mixture composition of 85 mol% ethanol and 15 mol% *n*-heptane, an ethanol material balance is used to determine the amount of extra ethanol to add:

$$100\,\text{moles} \times (50\,\text{mol\% ethanol}) + \text{A moles ethanol}$$

$$= \text{B moles} \times (85\,\text{mol\% ethanol})$$

$$100\,\text{moles} + \text{A moles} = \text{B moles}$$

Substituting the total mole balance for B into the first equation

$$50\,\text{moles ethanol} + \text{A moles ethanol} = (100\,\text{moles}$$

$$+ \text{A moles}) \times 85\,\text{mol\% ethanol})$$

$$\text{A} = 233\,\text{moles of ethanol added}$$

$$\text{B} = 333\,\text{moles total moles in new mixture}$$

The molar relative volatility of *n*-heptane to ethanol in the new mixture is

$$\alpha = \frac{y_1/x_1}{y_2/x_2}$$

where component 1 is *n*-heptane and component 2 is ethanol

$$= \frac{(0.30/0.15)}{(0.70/0.85)} = 2.4$$

The relative volatility of *n*-heptane over ethanol at ambient pressure is fairly low, which often results in inefficient batch strip-and-replace distillation. An alternative process in the form of constant-level distillation is a way to improve the time and material efficiency of batch distillation. Constant-level distillation will be discussed in detail in an upcoming section of the chapter.

12.2.1.4 Ternary Phase Diagrams Systems containing three components in vapor–liquid equilibrium are graphically represented in ternary phase diagrams, which are sometimes referred to residue plots. Unlike binary phase diagrams, these phase diagrams contain mostly information about the liquid-phase composition—hence the name residue plot—or in the case of vapor–liquid–liquid systems the liquid–liquid phase envelope with associated tie line end points defining the composition of each liquid phase. Examples of ternary-phase diagrams are shown in Figure 12.4 for a homogeneous azeotrope system and in Figure 12.5 a system with a heterogeneous azeotrope. Binary azeotropes are represented by points on the triangle edges labeled with the associated boiling point. Boiling points of individual components are included at the vertices of the triangle. When binary azeotropes are present, the ternary-phase diagram is divided into distillation regions separated by distillation boundaries. In the case of three or more binary azeotropes, ternary azeotropes may also form at the intersection of distillation boundaries. Pot composition trajectories are represented on the plot by residue curves that follow increasing temperature, either from one pure component vertex to another or between

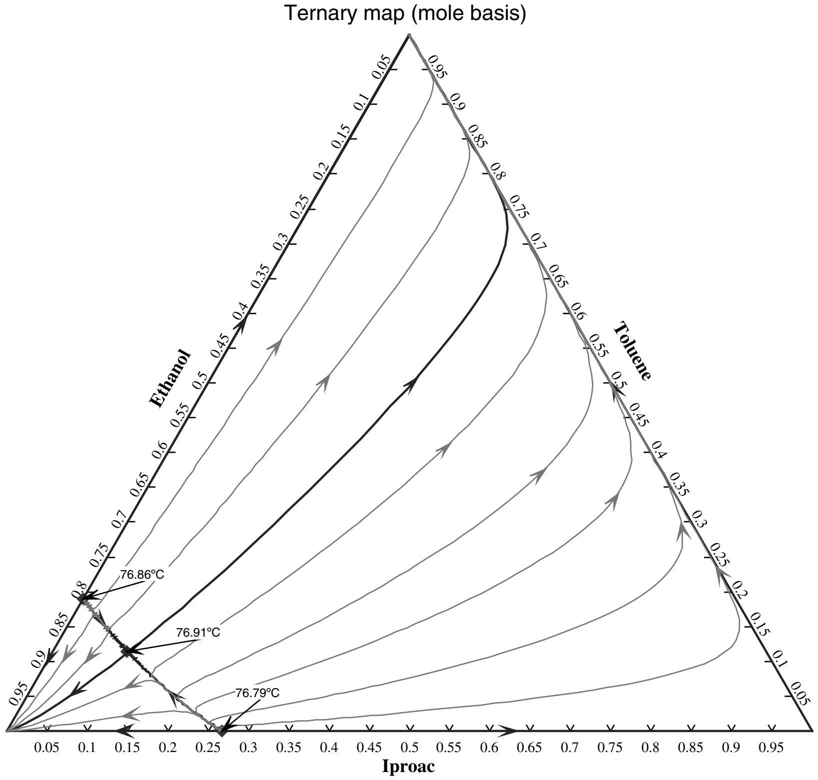


FIGURE 12.4 Ternary-phase diagram with homogeneous azeotrope.

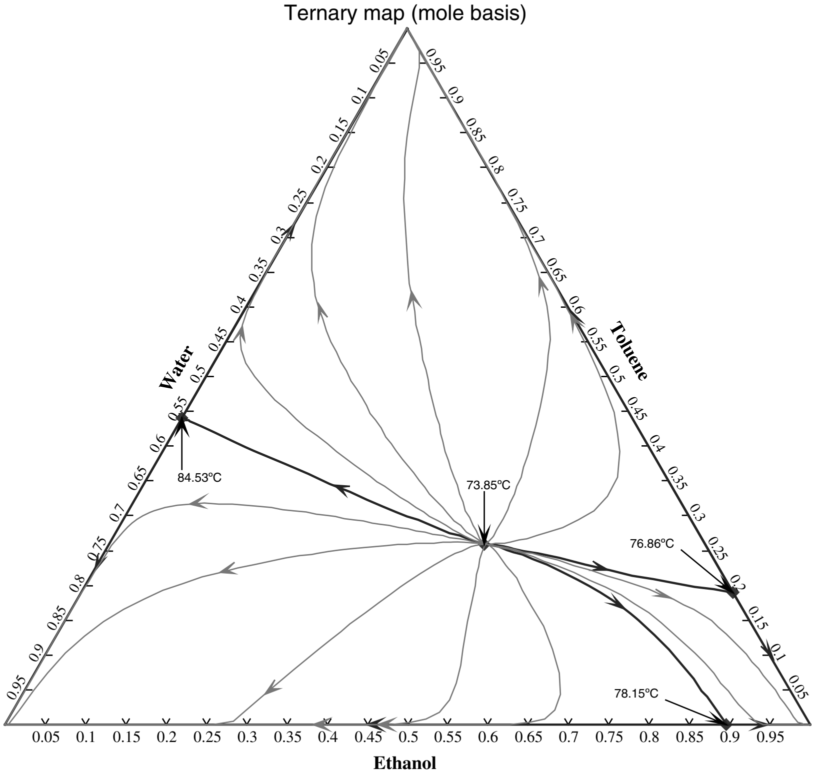


FIGURE 12.5 Ternary-phase diagram with heterogeneous azeotrope.

an azeotrope and a pure component. Analysis and design of distillation systems using ternary-phase diagrams can become complex with the number of possible scenarios posed by multiple binary and ternary azeotropes with and without liquid–liquid equilibrium phase envelopes, and there are many references available to consider for such in-depth analysis. As with binary diagrams, it is important for the chemical engineer to have access to the property data banks and plotting tools that allow quick access to system behavior in graphical form, which leads to a level of understanding for the purpose of process modeling and design that would be much more difficult and time consuming with the limitation of pure component boiling and perhaps binary azeotrope data at ambient pressure. These are the limitations imposed by tabulated data that can easily be overcome by computational tools such as Aspen Plus that provide flexibility in terms of depth of component choices and process conditions.

EXAMPLE 12.2 DISTILLATION OF ETHANOL AND WATER FROM TOLUENE

A 100 mole mixture of ethanol (63 mol%) and water (37 mol %) will be displaced with toluene at ambient pressure. Using the ternary VLE diagram in Figure 12.5, determine the moles of toluene that are added to reach the saddle ternary azeotrope near the center of the diagram. What is the significance of the mixture at this point? How much additional toluene is added to reach a starting distillation composition of 45 mol% toluene, 35 mol% ethanol, and 20 mol% water? Is this composition sufficiently high in toluene to ensure that distillation enriches the pot with toluene as distillate is collected from the condensed vapor?

Solution

A straight material balance line is drawn from the starting composition of 63 mol% ethanol and 37 mol% water to the toluene apex of the triangle. This line passes through the saddle azeotrope with a composition of 26 mol% toluene, 47 mol% ethanol, and 27 mol% water. A material balance on ethanol can be used to determine the total moles in the mixture at the saddle azeotrope

$$100\text{ moles }(63\text{ mol\% ethanol}) = \text{A moles }(47\text{ mol\% ethanol})$$

$$\text{A} = 134\text{ moles in total mixture at saddle azeotrope}$$

A material balance on toluene determines the amount of toluene added to reach the saddle azeotrope.

$$134\text{ moles }(26\text{ mol\% toluene}) = 34\text{ moles of toluene added}$$

The saddle azeotrope represents the ternary point of constant boiling composition at ambient pressure. The distillate and pot compositions will be equivalent during the entire distillation process. This can only be overcome by adding additional solvent. In this case, additional toluene is added to achieve a composition within the distillation boundary that favors ethanol and water volatility over that of toluene. The material balance line for toluene lies on the starting point of interest for the distillation. A material balance on ethanol between the toluene-free mixture and the desired mixture distillation starting point will determine the amount of toluene added:

$$100\ \text{moles}\ (63\ \text{mol\%}\ \text{ethanol}) = \text{B moles}\ (35\ \text{mol\%}\ \text{ethanol})$$

$$\text{B} = 180\ \text{moles of mixture at distillation starting point}$$

The amount of toluene in this mixture is

$$180\ \text{moles} - 100\ \text{moles} = 80\ \text{moles of toluene}$$

Therefore, the amount of toluene added past the saddle azeotrope is

$$\begin{aligned} &80\ \text{moles toluene} - 34\ \text{moles toluene} \\ &= 46\ \text{moles toluene added} \end{aligned}$$

The mixture pot composition will follow a residue contours interpolated from the figure toward the toluene apex of the ternary diagram.

12.2.2 Process Modeling and Case Studies

Chemical engineers designing distillation processes in the pharmaceuticals industry typically face the challenge of designing and optimizing single-stage equilibrium batch separations. These designs are further limited by the constraints of multi-purpose equipment also used for distillation. Absolute pressures in the equilibrium vessels and distillate receivers are limited to 0.05 bar–3 bar by the design limits of batch processing vessels and their associated vacuum pumping and pressure relief systems. Temperatures for the jacketed vessels and their associated condensers are often limited to the plant-wide heat transfer fluid service, or temperature control unit, service range of –20 to 150°C. Single-stage distillation is operated in two modes (1) strip and replace or (2) constant-level (or constant-volume). Strip-and-replace distillation is more common because it replicates the method used in the process development laboratory and does not require advanced control to operate on plant scale. However, constant-level distillation is beginning to gain favor for the benefits of improved solvent exchange efficiency for low relative volatility systems and for potential cycle time savings. The mathematical treatment of single-stage distillation is relatively easy for either mode, but speed of design is enhanced by the use of dynamic process simulators such as Aspen Batch Distillation, which is an adaptation of the more general dynamic modeler known as Aspen Custom Modeler. The scope of Aspen Batch Distillation goes beyond single-stage distillation, if needed, and also employs process control simulation, which is useful for implementing constant-level distillation models.

12.2.2.1 Strip and Replace Batch Distillation The more common mode of distillation in a pharmaceutical manufacturing facility is that of strip-and-replace distillation under ambient or vacuum conditions. This is achieved by stripping an initial mixture often containing a nonvolatile solute to a desired concentration or volume and then adding a replacement solvent to the equilibrium still or pot. Vapor is condensed into liquid distillate by an overhead condenser. Distillate is collected by gravity flow into a receiver that is usually similar in construction to the equilibrium still. The strip and replace procedure is repeated until a desired end point of composition and volume is obtained. Binary and ternary-phase diagrams are important references in the design of strip and replace batch distillation since the boiling point and azeotrope composition can have a significant impact on the efficiency of the operation. For instance, if a binary *T*-*xy* diagram is plotted with the composition of the undesirable solvent on the horizontal axis, the desired end point is toward the left-hand side of the plot. The pot residue will follow the path of increasing boiling point as the more volatile component is removed by vaporization and separated by condensation to the distillate receiver. If a minimum boiling azeotrope is present, then that path toward the higher boiling point may occur to the left or right of the azeotrope on the plot. In the standard plot with the undesirable solvent on the bottom axis, the desired direction is left; and therefore, the pot composition must be left of the azeotrope point for the pot to become enriched in the replacement solvent. Otherwise, on the right side of the azeotrope point, the replacement solvent will be lost through distillation. One solution to this problem is to add enough replacement solvent initially to reduce the mole or mass fraction to a point left of the binary azeotrope before beginning distillation to ensure the undesirable solvent has greater volatility than the replacement. Ambient pressure distillation is usually chosen for its simplicity, but vacuum distillation can be used to change the azeotrope composition of the system or reduce the operating temperature to preserve chemical stability of a solute.

Simple batch distillation is also known as differential distillation and has been described in mathematical terms by Lord Rayleigh and is derived as follows [2]. A charge of L_0 moles of liquid mixture is made to a still, which is heated to the boiling point at constant pressure. The initial composition for a given component of the liquid in the still has a mole fraction of x_1. As the liquid mixture boils at mole fraction x, the vapor V in equilibrium with the pot liquid is y, and this vapor is completely condensed to $y_d = x_d$. A material balance can be performed on this dynamic system for total moles.

$$\frac{dL}{dt} = -V \quad \text{(total material balance)}$$

or for a given component the material balance is

$$\frac{d(Lx)}{dt} = -Vy \quad \text{(component material balance)}$$

$$L\frac{dx}{dt} + x\frac{dL}{dt} = -Vy$$

If the above equation is combined with the total material balance

$$L\frac{dx}{dt} + x\frac{dL}{dt} = y\frac{dL}{dt}$$

Multiplying throughout by dt eliminates time dependence

$$Ldx + xdL = ydL$$

Rearranging L and mole fractions to either side

$$Ldx = (y - x)dL$$

or finally, the Rayleigh equation

$$\frac{dL}{L} = \frac{dx}{(y - x)}$$

A more useful form of the Rayleigh equation for numerical solution of time-independent batch distillation is

$$\frac{dx}{dL} = \frac{(y - x)}{L}$$

The values of y and x depend on knowledge of vapor–liquid equilibrium for a given system at temperature T and total pressure P.

This derivation describes composition trajectory of a solution during concentration in the batch still. If fresh replacement solvent is charged to the system, the new initial concentration can be determined by material balance and a composition new trajectory is then calculated again using the Rayleigh relationship. When a solute is present, one or more simplifying assumptions can be made when the nature of the solute in terms of mole fraction or binary interactions is unknown. The calculations may be performed ignoring the solute mole fraction and the results will be stated in terms of solvent fractions. This ignores the contribution of the solute as a mole fraction and presumes that the solute is nonvolatile. If solute is likely to impact boiling point temperature by the nature of its mole fraction in the solution, it may be included while still assuming the solute is nonvolatile, but this still ignores any binary interactions with solvent in the solution. Use of either assumption is reasonable for feasibility case studies or for initial design of the distillation process. The impact of a solute on vapor–liquid equilibrium could be assessed by estimation of binary interaction parameters for the NRTL model using COSMOthermX or group contribution methods such as UNIFAC, or ultimately measuring vapor–liquid equilibrium for the system in the laboratory with a range of compositions and concentrations. The latter is most time consuming and should only be used in the final stages of design of a commercial process.

EXAMPLE 12.3 BATCH STRIP-AND-REPLACE DISTILLATION WITH ETHANOL AND *n*-HEPTANE

A 100 L mixture of ethanol (65 wt%) and *n*-heptane (35 wt%) is added to a single-stage batch distillation vessel. Using a batch distillation simulator, determine the amount of ethanol that must be used in strip-and-replace distillation to achieve less than 0.1 wt% *n*-heptane at ambient pressure. The end point must be 100 L of final mixture, and the volume cannot exceed 200 L at any point in the distillation.

Solution

Using Aspen Batch Distillation, the simulation case is constructed for ambient pressure distillation of a single-stage system. The pot is filled with 100 L of 65 wt% ethanol and 35 wt% *n*-heptane. Next, 100 L of ethanol is added and distillation commences until a pot volume of 100 L is achieved at 77°C. An additional 100 L of fresh ethanol is added, and distillation resumes until 100 a pot volume of 100 L is achieved. After consuming 200 L of fresh ethanol in this operation, the pot contains 0.07 wt% *n*-heptane, which meets the requirement of achieving less than 0.1 wt% *n*-heptane by the end of distillation at a temperature of 78°C. In fact, the 0.1 wt% *n*-heptane specification was achieved at the 107 L mark. An additional 7 L of volume were distilled from the pot to achieve the final volume requirement of 100 L. *Note:* The volumes are approximate due to thermal expansion of solvents under ambient pressure distillation conditions.

12.2.2.2 Constant-Level Batch Distillation A variation of traditional batch distillation is constant-level distillation, which is sometimes referred to as constant-volume in this mode of operation. In this scenario, batch distillation takes place with a feed of fresh replacement solvent that matches the distillate rate in a fashion that maintains a constant liquid level in the equilibrium still. It is usually most efficient to concentrate the original solution to the greatest degree before adding replacement solvent, which minimizes the overall consumption of the added solvent to achieve the same end point. This effect is achieved my minimizing the amount of replacement solvent that is evaporated during the exchange. Analysis shows that systems with low relative volatility, $\alpha < 5$, enable replacement solvent savings of greater than 50% [3]. Constant-level distillation is an advance from traditional single-stage batch distillation efficiency when column rectification with reflux is unavailable. Distillation with partial reflux requires significant capital investment and results in increased batch cycle time and energy use. However, constant-level distillation may suffer inefficiencies without optimization of operating conditions. For instance, traditional batch strip-and-replace distillation uses a much larger fraction of the available heat transfer surface area in a vessel than constant-level distillation would under suboptimal conditions [4]. To maximize heat transfer area, the initially concentrated solution could be transferred by a suitably sized constant-level distillation vessel for batch processing in a full vessel. In a development or kilogram laboratory, constant-level distillation can be controlled by manual adjustment of replacement solvent flow that matches distillate collection. When volumes of solvent are small, the installation of advanced controls does not provide significant cost advantage. However, installation of level control would provide efficiencies in a pilot plant or commercial manufacturing facility under routine processing conditions. Automation enables programming of a defined end point in terms of replacement solvent volume charged. Level control can be maintained by a variety of inputs such as the still or distillate vessel level. Less direct due to differences in solvent density is the still or distillate mass measured by strain gauge as a control input. Beyond solvent exchange efficiency are the benefits of a reduced temperature profile over time experienced by the batch and reduced energy use by reduced solvent loading per batch. The reduced temperature profile may preserve chemical stability of solute leading to potentially higher yield and lower impurity loading in the isolated product.

EXAMPLE 12.4 CONSTANT-LEVEL DISTILLATION WITH ETHANOL AND *n*-HEPTANE

A 100 L mixture of ethanol (65 wt%) and *n*-heptane (35 wt%) is added to a single-stage batch distillation vessel. Using a constant-level distillation simulator, determine the amount of ethanol that must be used in constant-level distillation to achieve less than 0.1 wt% *n*-heptane at ambient pressure. The end point must be 100 L, which is identical to the starting mixture. Compare the amount of ethanol consumed in this example with that of the batch strip-and-replace distillation in Example 12.3, and determine which distillation method is more material efficient in this scenario.

Solution

Using Aspen Batch Distillation, the simulation case is constructed for ambient pressure distillation of a single-stage system. The pot is filled with 100 L of 65 wt% ethanol and 35 wt% *n*-heptane. The batch is heated to its initial boiling point of 72°C, and as distillate begins to collect, a level controller regulates the feed of fresh ethanol to the pot to maintain a 100 L volume. Distillation continues until 0.1 wt% *n*-heptane remains in the pot at a temperature of 78°C. The simulation shows that 150 L of fresh ethanol were consumed to achieve the *n*-heptane end point specification. The constant-level distillation processing scenario consumed 50 L less ethanol than the batch strip-and-replace distillation specified in Example 12.4. In the batch strip-and-replace scenario, 200 L of ethanol were consumed to achieve the 0.1 wt% *n*-heptane end point specification. Therefore, the constant-level distillation operation provided a savings of 25% of fresh ethanol used for strip-and-replace distillation. This level of savings is typical for scenarios in which the relative volatility of components is low.

12.2.3 Laboratory Investigation

12.2.3.1 Vapor–Liquid Equilibrium Data Collection As the number of possible binary combinations is quite large, a process developer or modeler is faced with screening and design without the benefit of binary interaction parameters for solvent pairs that are necessary to correlate activity coefficient for a given system as a function of composition and temperature. For instance, a selection of 100 solvents relevant to the pharmaceutical industry would provide 4950 binary combinations (100 × 99/2) among the set. Although the presence of a solute is often assumed to have negligible vapor pressure and minimal impact on the solution boiling point or vapor–liquid equilibrium of the system due to binary interactions, these assumptions may be ultimately tested in the laboratory. Accurate prediction requires careful measurement of important parameters in a laboratory equilibrium still. The experimentalist may choose to study binary systems for regression of collected data into binary interaction parameters, such as those for the NRTL model, that are temperature and composition dependent. Relying on Gibbs phase rule, the appropriate number of degrees of freedom is predetermined, and then the full condition of the system at equilibrium is recorded. Typically, in a binary system the pressure and total composition are predetermined and the batch is heated to its boiling point. At equilibrium, representative samples of vapor and liquid are extracted for analysis and system temperature is recorded. This data, converted to mole or mass fraction versus temperature, is then regressed within a convenient platform such as Aspen Properties into the a_{ij}, a_{ji}, b_{ij}, b_{ji}, and c_{ij} parameters (as subparameters of α_{ij} and τ_{ij}) of the NRTL model for later use in system phase diagramming and process modeling. Applications designed for regression of such data also conveniently perform thermodynamic consistency testing with the ability to exclude data points that are inconsistent for the system. Thermodynamic consistency testing is derived from the Gibbs–Duhem equation [5].

$$\sum x_i d\ \ln\gamma_i = 0$$

There are two derived forms for thermodynamic consistency testing based on the Gibbs–Duhem equation. First, the integral test is [6]

$$\int \ln\frac{\gamma_i}{\gamma_j}dx_i = 0$$

Graphically, the net area under a plot of $\ln(\gamma_i/\gamma_j)$ versus x_i must equal zero, or typically to some tolerance such as 10%.

Alternately, a differential or point test that tests consistency at a single composition may be constructed from the same equation and subjected to a tolerance similar to the integral test [7].

$$\frac{d\ln\gamma_j^{\circ}}{dx_j} = -\frac{x_i}{1-x_i} \times \frac{d\ln\gamma_i^{\circ}}{dx_j}$$

Graphically, the slopes of a combined plot of $\ln\gamma_i$ and $\ln\gamma_j$ versus x_i at a given composition must satisfy the equation to establish thermodynamic consistency. The results of consistency tests speak nothing about the accuracy of the data; only that it fits within the bounds imposed by partial molar Gibbs free energy of components, or chemical potential, within a system at equilibrium.

12.2.3.2 Batch Distillation Simulation in the Laboratory Performing batch distillations in the laboratory as part of process development is not a trivial exercise if reliable scale-up to manufacturing conditions is the goal. Lab-scale distillations should be studied in equipment representative of a single-stage still on scale, with the ability to collect samples of off-line analysis or insert analytical probes. The equipment must be adequately insulated from ambient conditions to prevent condensation and liquid holdup in places other than the condenser and distillate receiver, respectively. In either strip-and-replace or constant-level distillation, an accurate material balance and associate parameters should be used to record and describe the procedure. The total amount of replacement solvent consumed until the end point of the distillation is important as well as the liquid volumes and compositions in the still and the distillate receiver. A temperature profile should be noted as it may have a direct impact on product quality since distillation time on scale will be longer than in the laboratory. Vacuum distillations should be simulated by first applying vacuum to a desired set point that matches plant capacity, and then slowly applying heat to reach the solution boiling point to mimic common practice in manufacturing facilities. This practice also reduces the likelihood of bumping or boiling over of pot contents into the receiver. Unintended refluxing before the condenser will result in a distillation with higher efficiency than achievable in a single-stage on scale. During distillation development, other effects such as foaming or solute oiling should be noted. Uncontrolled crystallization of the solute may occur at any pressure during distillation, which may impact the quality of the isolated product by incorporating impurities or producing an undesired polymorph. Finally, an important simulation for batch distillation is that of extended time at a given temperature, whether it is the initial or final boiling point. The final boiling point will be higher that the start, so this will represent the most stressed condition in terms of chemical stability in the still. Stability at final reflux temperature is often tested for at least 24 h and sometimes longer to check for degradation that may occur on scale due to extended processing time or unexpected delays. The heat transfer efficiency of the plant will also determine the time to heat up and cool down the solution before and after distillation and this temperature history must be incorporated into the design. Similarly, there may also be heat and cool cycles associated with requirements around minimum temperature for sampling or solvent charging that should be considered.

12.2.4 Process Scale-Up

12.2.4.1 Equipment Selection The selection of equipment for batch distillation is normally limited in the pharmaceutical industry due to the design of synthesis plants around the strategy of maximum flexibility. Therefore, equipment selection is about choosing single-stage vessels appropriate for the task, which is to efficiently concentrate or exchange solvents without impacting the quality of pharmaceutical intermediates or active ingredients carried through. Efficiency is about choosing the volume of vessel that provides maximum heat transfer area per unit volume and with a minimum stir volume that meets the needs of the process. Further, a system capable of vacuum or pressure should be chosen carefully when necessary to achieve a distillation target. The vacuum and pressure limits should be well understood and the heat removal performance of the condenser in terms of operating temperature should be noted. If a constant-level distillation is planned, the replacement solvent should be added to the still in a fashion that allows rapid mixing with the batch. In other words, avoid adding the replacement solvent in such a way that it runs down the heated wall of the vessel and has opportunity to vaporize before mixing with the contents of the still.

12.2.4.2 Process Control and Unit Operation In operation the batch still requires temperature and perhaps vacuum control. In the mode of constant-level distillation, the replacement solvent feed and distillate rates must be matched with appropriate automation. For temperature control, the most beneficial mode of operation is temperature differential across the jacket to maintain vessel integrity and to preserve solute chemical stability by keeping the temperature at the vessel wall below a reasonable specification. A typical temperature differential set point is less than 30°C to achieve a desirable boil up rate at a given pressure. In this regime, the temperature of the jacket will increase with the boiling point to maintain the specified temperature differential through the distillation end point.

12.2.4.3 End Point Determination The desired end point distillation is usually based upon a desired solution composition or complete displacement of one solvent from the system. Detection of this end point is available through a variety of direct or indirect measurements that can be made on or off line. Sampling of the still contents for off-line solvent analysis is the most direct and most likely option in most pilot and manufacturing scale facilities. However, the turnaround time for results may be on the order of hours and sampling may require cooling of the batch to a safe temperature. Sometimes the batch temperature is a sufficient end point when a complete exchange of solvents is desired and the downstream process is insensitive to the presence of small amounts of the replaced solvent or water. In that case, the operator would continue distillation until the pot temperature reaches the boiling point of the pure solvent or that of the solution tested in the laboratory since the presence of a solute, which can raise the boiling point by $\geq 1°C$. If the distillation is run under vacuum, it is useful to provide boiling point data at the desired system pressure as a guide to distillation end point. Note that heterogeneous mixtures will exhibit a constant temperature boiling point until the mixture becomes homogeneous. From that point, there is often a rapid increase in temperature to the replacement solvent end point.

12.3 DESIGN OF EXTRACTION OPERATIONS

12.3.1 Liquid–Liquid Equilibrium Modeling

Equilibrium-phase models for the liquid–liquid case requires demonstration of equivalent fugacity in each phase for each component, and this case may be extended further by the inclusion of vapor-phase equilibrium. As with VLE, laboratory measured data is the preferred source of equilibrium data, and even without the facility to determine liquid–liquid equilibrium parameters directly, one may rely on well-populated data banks of NIST, DIPPR, and DETHERM for raw data. Or, as with VLE, the liquid–liquid equilibrium data may be estimated by computational tools such as COSMOthermX and activity coefficient data may be extracted for regression into nonideal solution models such as NRTL. With binary interaction parameters in hand, one may begin to plot liquid–liquid phase diagrams that are descriptive for binary or ternary systems. Higher order systems may be modeled easily with the binary interaction parameters even though graphical representation of equilibrium between four or more components is not as helpful.

12.3.1.1 Binary Activity Coefficient Data Focusing here on the liquid–liquid case alone, the important temperature and composition dependent element of equilibrium is the activity coefficient of each component of each phase. As discussed previously, a variety of nonideal solution models may be used to correlate activity coefficients for components as a function of temperature and composition, and in the case of liquid–liquid equilibrium the NRTL model is preferred because of the flexibility in the description of liquid-phase splitting as well as VLE. Equilibrium-phase splitting is only possible in nonideal solutions with significant deviations in the activity coefficient for each component away from unity.

12.3.1.2 Phase Diagrams The primary method of graphical representation of liquid–liquid equilibrium between three components is a ternary-phase diagram. There are several methods for plotting three-component liquid equilibrium, and the most common method is a triangular plot as shown in Figure 12.6. The plot may be formatted as an equilateral or isosceles triangle with the sides of either format divided as mole or mass fraction of each of the three components. Within the bounds of the triangle edges, a boundary line is drawn to divide single- and two-phase regions for a mixture of three components. Tie lines within the two-phase envelope determine the equilibrium mole or mass fractions of each component in each liquid phase at a given temperature. As liquid–liquid equilibrium is also temperature dependent, the size and shape of the two-phase region will be affected by changes in temperature. The point at which the tie lines become infinitely small is known as the plait point, where both liquid phases have identical compositions at their limit of immiscibility.

EXAMPLE 12.5 EXTRACTION OF ACETONE FROM WATER INTO TOLUENE

A 100 mole mixture of acetone (70 mol%) and water (30 mol %) is added to an extraction vessel. Determine the minimum number of moles of toluene must be added to the system to obtain a liquid–liquid system in equilibrium. Further, how much additional toluene must be added to the system to obtain a liquid–liquid system with the light phase containing 45 mol% acetone. What is the mole composition of the light and heavy phase in equilibrium at 20°C? Finally, determine the molar distribution coefficient of acetone and the selectivity of toluene for acetone relative to water in the final mixture.

Solution

Use the ternary-phase diagram in Figure 12.6 for the toluene, water, and acetone system to determine behavior of a ternary mixture of these solvents. A straight line drawn from the 70 mol% acetone and 30 mol% water intersection to the 100% toluene apex of the triangle determines the composition path for the addition of pure toluene to the system. The straight line intersects the phase boundary at 23 mol% toluene, 54% acetone, and 23% water. Performing a mole balance on acetone, we have

100 moles × (70 mol% acetone) − A mol × (54 mol% acetone) = 0; A = 130 moles of mixture after toluene

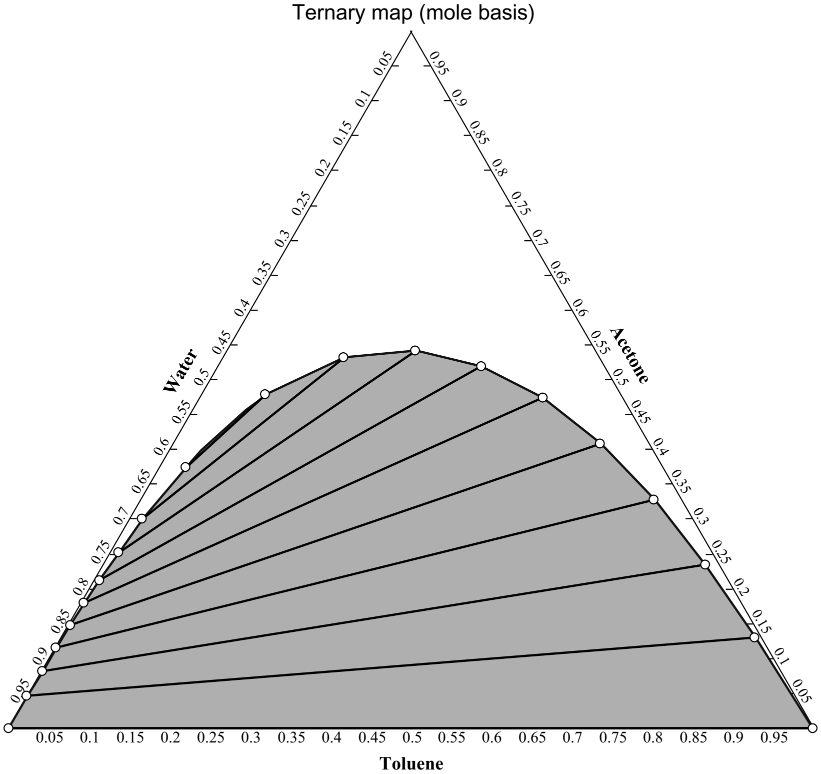


FIGURE 12.6 Ternary liquid–liquid equilibrium-phase diagram.

is added to the point of phase separation. A balance on toluene on the mixture shows

130 moles × (23 mol% toluene) = 30 moles of toluene added to reach the beginning of phase separation at 20°C.

A tie line is constructed at the intersection of 45 mol% acetone, 46 mol% toluene, and 9 mol% water to the other side of the phase boundary at 17 mol% acetone and 83 mol% water. This tie line intersects the composition path line at 40 mol% toluene, 42 mol% acetone, and 18 mol% water. Performing another acetone mole balance, we find

100 moles × (70 mol% acetone) – B mol × (42 mol% acetone) = 0; B = 167 mol total mixture.

The total amount of toluene in this second mixture is

167 moles (40 mol% toluene) = 67 mol toluene

The amount of extra toluene added beyond the initial phase split is

67 moles – 28 moles = 39 moles of toluene added in total

The compositions of the two phases in equilibrium based on the end points of the phase envelope tie line are

45 mol% acetone, 46 mol% toluene, and 9 mol% water (light phase)

17 mol% acetone, 83 mol% water, and trace toluene (heavy phase)

The molar distribution coefficient of acetone in terms of light-to-heavy phase compositions is the ratio of the mol% of acetone in the toluene phase divided by the mol% in the aqueous phase:

$$\frac{x_{a,l}}{x_{a,h}} = \frac{45\ \text{mol\%}}{17\ \text{mol\%}} = 2.65$$

where component 1 is acetone in the light phase and component 2 is acetone in the heavy phase.

A ratio greater than unity indicates the equilibrium distribution of acetone is favored in the light phase, which contains the most toluene. The selectivity of the light phase for acetone is equal to the distribution coefficient divided by the distribution coefficient of water between phases:

$$\beta = \frac{2.65}{(x_{w,l}/x_{w,h})} = \frac{2.65}{(9\ \text{mol\%}/83\ \text{mol\%})} = 24.4$$

This is a relative measure of the propensity of toluene to extract acetone while accounting for the amount of water taken by the light phase in the extraction. A higher selectivity is desirable to achieve efficient exchange of a cosolvent between liquid phases in equilibrium.

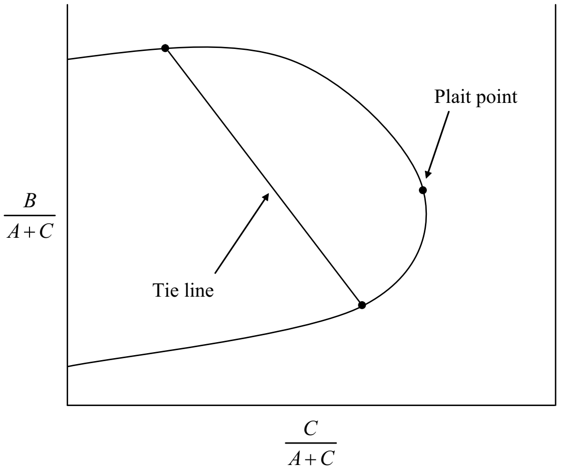


FIGURE 12.7 Ternary equilibrium phase diagram in Janecke format.

An alternative to triangular form for the ternary diagram is a Janecke plot on rectangular coordinates, as demonstrated in Figure 12.7. The rectangular plot contains the same amount of information as the triangular plot although not as direct, since each axis is a ratio of component fractions rather than pure component fractions. Another feature of interest on a ternary-phase diagram is the tie line that represents an equilibrium mixture in which each phase is of equal density, which may therefore present challenges in phase separation. This is referred to as the isopycnic line and is usually represented by a dashed line on the phase diagram.

Distribution and selectivity of solute between the extract and raffinate phases is of interest in the selection of solvents and design of extractive systems. Figure 12.8 is a demonstration of distribution plots of a solute between two liquid phases. The 45° line represents the boundary of unity in the distribution coefficient. The distribution curve ends at the plait point for the system. In some systems, the distribution curves may cross the 45° line before ending at the plait point. Such a system is referred to as solutropic because the distribution passes through unity. On a triangular ternary plot, the slope of tie lines changes sign in solutropic systems, which may also pose challenges in the design of a liquid–liquid extraction system.

12.3.2 Process Modeling and Case Studies

Similar to the case of batch distillation, liquid–liquid extraction processes in the pharmaceutical industry involving solutes of moderate manufacturing volume and high value are typically operated as single-stage operations in multipurpose manufacturing vessels. Multistage extractors present an opportunity for efficient separation of a solute from a given phase when the distribution coefficient with a given solvent is small. However, significant investment in processing equipment and control systems may be required for multistage systems, whereas a single-stage extraction is easy to operate in flexible plant equipment at hand.

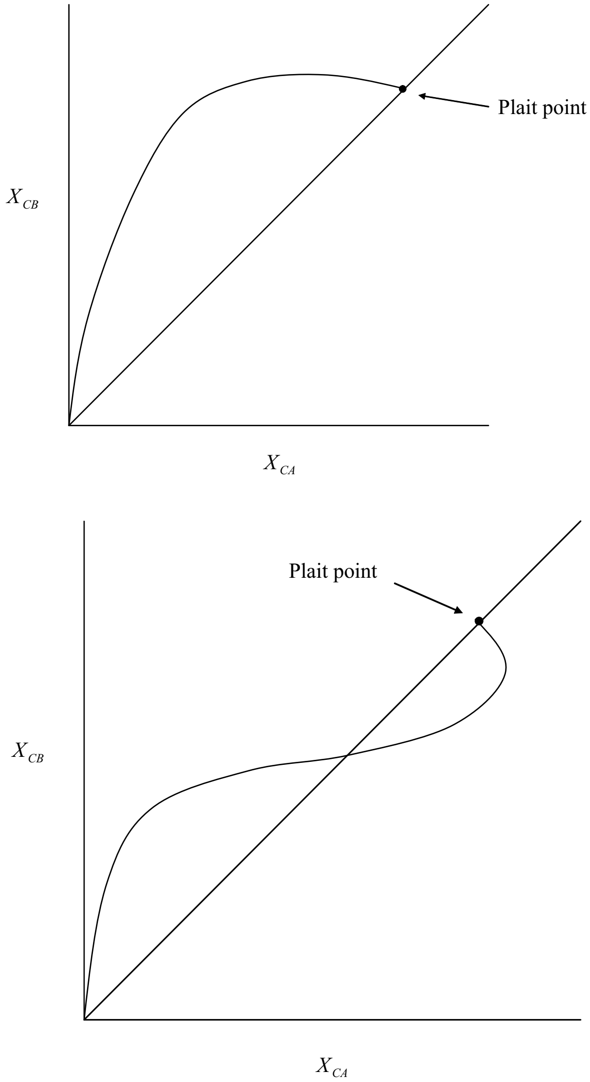


FIGURE 12.8 Liquid–liquid distribution curves.

12.3.2.1 Single-Stage Extraction A single-stage liquid–liquid extraction may be performed in the same bulk vessel used for most other operations in the batch pharmaceutical plant. The temperature range of −15 to 150°C in these jacketed vessels provides plenty of flexibility in the design of liquid–liquid extraction. Phase equilibrium operations such as this are easily modeled in a process simulator such as Aspen Plus using a decanter (LLE) or three-phase flash (VLLE) model. Temperature and overall composition are required inputs, and results are posted in terms of mass or mole fraction plus total mass and volume for each resulting liquid phase. If liquid-phase splitting will not occur under the specified conditions, only a single liquid stream flow and composition is reported. Case studies are easily generated by creating sensitivity plots or by running optimization routines for parameters of interest such as temperature or solvent volumes. These models rely on accurate prediction of activity coefficients through a nonideal solution model such as NRTL, with temperature-dependent parameters stored in model data banks. Aspen Plus may also be used to generate triangular ternary-phase plots for liquid–liquid equilibrium systems as a function of temperature. Multiple single-stage contactors can be linked in series with fresh solvent input to each block to model multiple extraction operations. The results of multiple single-stage operations will differ from the countercurrent operation known as multistage extraction.

EXAMPLE 12.6 MULTIPLE SINGLE-STAGE EXTRACTION OPERATIONS

Using the starting mixture from Example 12.5 of acetone (70 mol%) and water (30 mol%), determine the final composition of the light phase if the initial mixture and two intermediate heavy phases are each contacted with 67 moles of fresh toluene in a series of single-stage extractions at 20°C.

Solution

Either the ternary liquid–liquid equilibrium-phase diagram for the toluene–acetone–water system shown in Figure 12.6 or a process simulator such as Aspen Plus may be used to determine the outcome of this series of single-stage extractions. In Aspen Plus, a series of three DECANT blocks would be linked by the heavy-phase streams, and each DECANT block. Equal amounts of fresh toluene are fed to each DECANT block. The first stage extraction mixes 100 moles of acetone (70 mol%) and water (30 mol%) with 67 moles of fresh toluene. At equilibrium, the first stage phases contain

Light phase: 146 moles (45.9 mol% toluene, 45.5 mol% acetone, 8.6 mol% water)

Heavy phase: 21 moles (0.4 mol% toluene, 17 mol% acetone, 82.6 mol% water)

The second stage receives the heavy phase from the first stage and 67 moles of fresh toluene. At equilibrium, the second stage phases contain

Light phase: 71 moles (95.0 mol% toluene, 4.7 mol% acetone, 0.3 mol% water)

Heavy phase: 18 moles (trace toluene, 1.7 mol% acetone, 98.3 mol% water)

Finally, the third stage receives the heavy phase from the second stage and 67 moles of fresh toluene. At equilibrium, the third stage phases contain

Light phase: 67 moles (99.4 mol% toluene, 0.4 mol% acetone, 0.02 mol% water)

Heavy phase: 18 moles (trace toluene, 0.14 mol% acetone, 99.86 mol% water)

In three single-stage extractions with a total of 201 moles of fresh toluene, the acetone in the water was reduced to 0.1 mol%. The heavy, aqueous phase contains only 0.002 moles of toluene, but the combined light, organic phases contain a total of 12.8 moles of water, which is 42% of the original 30 moles of water in the initial feed. Although toluene extracts acetone very well from water, this system is not very selective for acetone because a significant amount of water is extracted into the light, organic phase as well.

12.3.2.2 Multistage Countercurrent Extraction The use of multiple stage countercurrent extraction to improve the efficiency of liquid–liquid extractions is easily modeled by most process simulators. In multistage countercurrent extraction, feed and solvent streams enter opposite ends of the column. The product streams exiting the column are the extract and the raffinate. The extract stream contains the solvent with the desired component transferred between phases, whereas the raffinate is the stream remaining after the desired component is transferred to the extract. The internals of a multistage countercurrent extraction column can be quite varied. Stages are formed by zones of intense mixing between independent liquid phases, and this is accomplished by column packing in a variety of configurations (structured or random), by mechanical agitators such as those seen in Scheibel, Karr, or rotating disk columns, or by liquid dispersion with static sieve trays. Regardless of the liquid phase contacting technology, the important characteristic for a given column operating under specific temperature and flow rate conditions is the number of equivalent equilibrium stages the equipment achieves. If the equilibrium behavior of component distribution between phases is well understood and mapped with the aid of a ternary diagram or expressed in fundamental terms of activity coefficient model binary parameter terms, a process model may be used to explore operating conditions. The inputs for the model block are identical to that single-stage operation, except that the total number of equilibrium stages must also be specified. The results obtained from this countercurrent phase contacting scheme are reported in the same fashion as the single-stage model. Example 12.7 demonstrates the difference in efficiency based on choice of countercurrent multistage extraction in place of the multiple single-stage operations shown in Example 12.6.

EXAMPLE 12.7 MULTISTAGE COUNTERCURRENT EXTRACTION

Using an acetone (70 mol%) and water (30 mol%) feed equivalent to that of Example 12.6 (100 moles/h), determine how many moles of fresh toluene must be fed to a three-stage countercurrent extraction column at 20°C to achieve 0.14 mol% acetone in the heavy, aqueous phase at the outlet of the extraction column.

Solution

An Aspen Plus simulation is a convenient manner of solving this type of multistage extraction problem, although graphical methods using an equilibrium and operating line approach for staged operations may also be used to solve this type of problem. In Aspen Plus, the EXTRACT column model is used to simulate the countercurrent contact of the heavy feed stream entering the top of the column with a feed of fresh toluene entering the bottom of the column. Three equilibrium stages and adiabatic operation are specified for the model. The feed to the top of the column is 100 moles/h in total containing 70 mol% acetone and 30 mol% water at 20°C. The objective of the simulation is to add only enough fresh toluene to achieve 0.14 mol% acetone in the aqueous raffinate stream at the exit of the bottom of the column. This can be achieved by trial-and-error manipulation of the fresh toluene feed while monitoring the raffinate composition, or in Aspen Plus a design specification algorithm may be specified to manipulate the toluene feed rate with the objective set at the specified acetone composition in the raffinate. If design specification is used to solve the problem, the solution is to feed 48.5 moles/h of toluene to the column to achieve 0.14 mol% acetone in the aqueous raffinate. In this countercurrent extraction example, 20.5 mole/h of water are extracted by the fresh toluene compared with 12.8 moles of water in the previous example. This represents a loss of 68% of the total water fed to the column. The raffinate contains 0.001 moles/h of toluene, however, which is as low as the loss of toluene observed in Example 12.6. The most striking result, however, is that the countercurrent column requires only 48.5 mole/h of toluene compared with the multiple single-stage operation that requires 201 moles of fresh toluene. This represents 24% of the toluene requirement compared to the multiple single-stage operation.

12.3.3 Laboratory Investigation

The design of liquid–liquid extraction operations in the development laboratory may be divided generally into equilibrium data collection and operation stressing. Both require effective lab-scale equipment to provide robust data and scale-up assessment on the way to the design of an efficient process, whether single or multistage extraction is the objective.

12.3.3.1 Equilibrium Data Collection Liquid–liquid equilibrium data is often collected in a single-stage cell in which conditions such as temperature and total composition are altered to allow measurement of phase equilibrium across a wide operating space. An accurate representation of equilibrium data relies on accurate analytical measurement of individual phase compositions. The cell is loaded with components and agitated sufficiently to increase the surface area between the dispersed and continuous phases. The surface area between phases is the mass transfer area across which components distribute between phases to an equilibrium condition. Sufficient time must be given to ensure an equilibrium condition is met, and a time series of phase samples should be analyzed to ensure a constant value is obtained in the absence of some interfering form of component degradation. After equilibrium is achieved, agitation is stopped and the resulting phases are allowed to split into individual layers. In some cases only a single homogeneous solution may result, or sometimes relatively stable emulsion may form between phases. Both of these conditions signify a combination of components that is unsuitable for use in liquid–liquid extraction, since the goal of separation is not achievable at a given temperature and total composition. Data collected in the laboratory with the single-stage equilibrium cell is used to provide the basis for a ternary-phase diagram or for regression of binary interaction parameters of activity coefficient model such as NRTL. An early indication of unit operation behavior in terms of relative difficulty of phase separation by settling, the accumulation of interfacial contaminants, or potential component degradation can be observed and recorded during equilibrium data collection. That is, the experience obtained in equilibrium data collection may bring insight into the behavior of the system upon scale-up to manufacturing.

12.3.3.2 Extraction Laboratory Simulation Single or multistage laboratory models may be easily constructed to further assess behavior of system components under the conditions of interest and to refine those conditions to optimize the desired separation. Single-stage laboratory models are easiest to construct since they are close to the equilibrium cell described previously. In fact, there is no reason that a single-stage model could not be used for the purpose of gathering equilibrium data. The single-stage model incorporates several elements in terms of geometry and agitation conditions that mimic and which will be encountered on scale for the purpose of providing a close scale-down representation of manufacturing technology. In the pharmaceuticals industry, this is typically the same batch vessel used for other unit operations such as reaction, distillation, and crystallization. In addition to providing equilibrium data, the single-stage model should be used to examine and understand the dynamic approach to the equilibrium state. One can examine the impact of agitator choice and the power applied at the blade tip, where the highest shear forces are found, to determine the propensity for the system to irreversibly emulsify. The position of the agitator relative to vessel fill height is also an important factor in the extraction efficiency and approach to equilibrium. A system with a large difference in densities between phases may make efficient mixing difficult to achieve with an agitator set low in the vessel as is often the case in pharmaceutical manufacturing facilities for the purpose of enabling low stirring volumes. Multiple-stage models are scaled-down versions of the manufacturing scale in terms of the intended phase mixing technology. A direct scale-down of the contacting technology is necessary to ensure that the dynamic and equilibrium behavior of the components in the system behave in a desirable manner. These scaled-down systems are typically constructed of glass-walled columns to allow easy visibility of conditions within the operating space. This allows the user to observe the presence of emulsions or the accumulation of solid particulate or oily components within the equilibrium stages that could impact extraction efficiency or the mechanical operation of the system over an extended operating time.

12.3.3.3 Phase Split Efficiency The rate of phase separation is important to ensure an efficient operation of the extraction process. Since it is difficult or impossible to see into manufacturing-scale equipment to assess the quality of the liquid-phase splitting, the predicted time to phase separation on manufacturing scale must be known or inferred from laboratory behavior.

12.3.3.4 Impact of Missed Phase Splits and Desired Fate of Phase Interface The process designer must specify the desired fate of the phase interface to ensure proper operation of liquid–liquid extraction as a separation technique. In other words, the designer must state explicitly which phase must be disposed of entirely while keeping in mind that a small amount of one phase will always be carried with the other as a result of a phase split. Even after specifying the phase split strategy with regard to the interface after a batch liquid–liquid extraction operation, it is important to test the outcome of the reversed condition, or in other words a missed phase split on subsequent extractions, downstream operations, or perhaps process yield. Use the resulting product phase containing a small amount of the waste phase, and any associated rag material in downstream operations and note any impact on the process. If the impact is significant, then the phase split strategy or other specification may be enhanced to limit the extent of potential downstream problems.

12.3.3.5 Difficult Separations In some cases of liquid–liquid extraction, ease of dispersion is less of a problem than separating the resulting liquid phases after components are distributed in an equilibrium state. In the worst case, the dispersed phase remains stable as an emulsion, and this is a terminal condition to avoid. There are generally three physical properties of components and their mixtures that determine the relative ease of separation after equilibrium extraction and those are (1) liquid-phase density differences, (2) viscosity, and (3) interfacial tension. A large density difference between resulting phases enhances the rate of phase settling, while a low viscosity of the continuous phase also promotes separation. Moderate interfacial tension between the dispersed and continuous phase allows relatively easy separation to take place by coalescence of droplets but equally it does not hinder the dispersion of one liquid phase into another.

Occasionally an emulsion cannot be avoided due to the nature of the system or due to the batch variability in manufacturing. During process design or in a manufacturing environment, there are several methods of handling emulsified phases to recover the phase separation. Sometimes an interfacial particulate or rag layer may be responsible for stabilizing an emulsion, and its influence on the system may be tested by filtering the mixture to remove the material. The phases may separate as expected in the absence of this material. The other technique is to alter the physical properties of phases mentioned previously in a manner that benefits the rate of separation. For instance, density and interfacial tension of an aqueous layer can be increased by the addition of inorganic salts. These salts will also serve to reduce the solubility of water in the organic phase that is a common contributor to emulsification. An increase in temperature will typically reduce the continuous phase viscosity to further improve separation. Finally, a mechanical means of increasing the gravitational force, such as a centrifugal separator, can be used to increase the rate of sedimentation of the dispersed phase. Increasing the volume of the dispersed phase relative to the continuous phase may also accelerate coalescence of droplets to aid separation.

12.3.3.6 Process Scale-Up The selection of scale-up equipment and process controls should be considered as laboratory process development activities near completion. The primary objectives of the liquid extraction scale-up design should be to achieve time and material efficient separation and purification of components.

12.3.3.7 Equipment Selection Two factors for consideration are the agitator type and fill level of the vessel for efficient equilibrium mixing. Most general-purpose vessels have agitators placed relatively low to the maximum fill volume. If the densities of liquid phases are significantly different and the vessel is nearly full, the time to equilibrium during agitation may be extended. High-shear agitator types and vessel baffles make this operation more efficient under these conditions.

12.3.3.8 Process Control The most common parameter under adjustment and control in liquid–liquid extraction other than temperature is pH, which is often adjusted with aqueous acid or base. An adjustment in pH is used to convert the component of interest into a free acid, free base, or salt to enable it to distribute preferentially into a desirable liquid phase for further processing. The acid or base is added to the agitated solution and the pH is either measured by a probe installed in the tank or in a recirculation loop. Alternatively, a sample of the mixture or aqueous phase may be taken from the vessel for off-line analysis. The pH specification for a process should be carefully defined with regard to the state of agitation. The pH measurement of an aqueous and organic liquid-phase mixture results in a different pH value than measurement of the aqueous phase alone. Temperature also impacts solution pH and this effect must be accounted for when taking a sample for off-line analysis.

12.3.3.9 Unit Operation Maximum agitation is most often a benefit to liquid–liquid extraction operation since impeller shear creates interfacial surface area between phases. Greater the surface area between phases means increased mass transfer rates toward the equilibrium state. On a manufacturing scale in a batch pharmaceutical plant, the agitator is typically set very low to achieve stirring at very low volumes. This can hinder liquid–liquid extraction when the vessel is more than half full, since the upper portions of the fluid are less turbulent and coalescence between dispersed droplets is more likely. Using an impeller types with greater shear characteristics may assist the operation by ensuring the formation of minimum droplet size near the impeller. Where one impeller would be damaging in a crystallization process, the same impeller would typically improve liquid–liquid extraction performance. Once equilibrium is achieved, agitation is stopped, and the phases are allowed to settle into top and bottom layers.

12.3.3.10 Phase Split Determination Separation of phases from a single-stage extractor is usually achieved by draining the lower layer from the vessel through a bottom valve. The end point of the phase split is normally determined by visual inspection through a sight glass near the bottom valve. The sight glass allows detection of the interface between phases. When there is color similarity between phases, a conductivity probe may also be used in conjunction with the sight glass to detect the step change in conductance between phases as the split is nearing completion. The aqueous phase normally has greater conductivity than the organic phase and change between phases with the sensor is either indicated by the change in a signal light or displayed by digital indication of the conductivity measurement.

12.A APPENDIX

12.A.1 Guide to Generation of Binary Interaction Parameters for Solvent Pairs

12.A.1.1 Software COSMOthermX v.C21 and Aspen Properties V7.1 (or Aspen Plus V7.1).

12.A.1.2 Purpose This guide provides instruction on the generation of NRTL binary interaction parameters (BIPs) for liquid compounds pairs using COSMOthermX and Aspen Properties. Once the appropriate data are in Aspen Properties, they can be used as the basis for distillation or liquid–liquid extraction modeling. Estimation of BIPs through COSMOthermX is only required if the NRTL binary interaction parameters are not predefined in the Aspen Properties data bank. This guide assumes the user has basic skills in operating COSMOthermX and Aspen software packages.

12.A.1.3 Procedure The flowchart in Figure 12.9 describes the workflow for generating BIPs using COSMOthermX and Aspen software interfaces. The workflow demonstrates three paths to estimates for BIPs, and each is ranked by the accuracy of results based on the complexity of inputs used for estimation. The rankings for NRTL parameter estimation are summarized here:

- *Good*: Provides a set of *infinite dilution* activity coefficients for a pair of components at a *single temperature*. The NRTL parameters are estimated within Aspen.
- *Better*: Provides NRTL parameters directly from COSMOthermX, but the *parameters are insensitive to temperature* and are generally applicable to the pressure or isothermal conditions chosen in COSMOthermX.
- *Best*: Regression of activity coefficients from COSMOthermX is performed within Aspen to provide *temperature-dependent* NRTL parameters within Aspen.

Screenshots from both applications are shown after the flowchart as further guidance on the process. After determining the desired path through the workflow, the user should proceed to the matching workflow section of the guide for step-by-step instructions. A methanol–water system is used throughout the examples. A comparison of results for three binary solvent systems is also provided at the end of the section.

Estimation of NRTL BIPs from COSMOthermX infinite dilution activity coefficients

1. In COSMOthermX, choose the Activity Coefficient tab in the interface (Figure 12.10).
2. Select the temperature for the infinite dilution activity coefficient estimation (gamma).
3. Check the “Pure” box for each solvent and “Add” and “Run” the cases.
4. Examine the output from the COSMOthermX in terms of Ln(gamma) (Figure 12.11).
5. Convert the results to values of gamma for each solvent by calculating the exponential value of each.

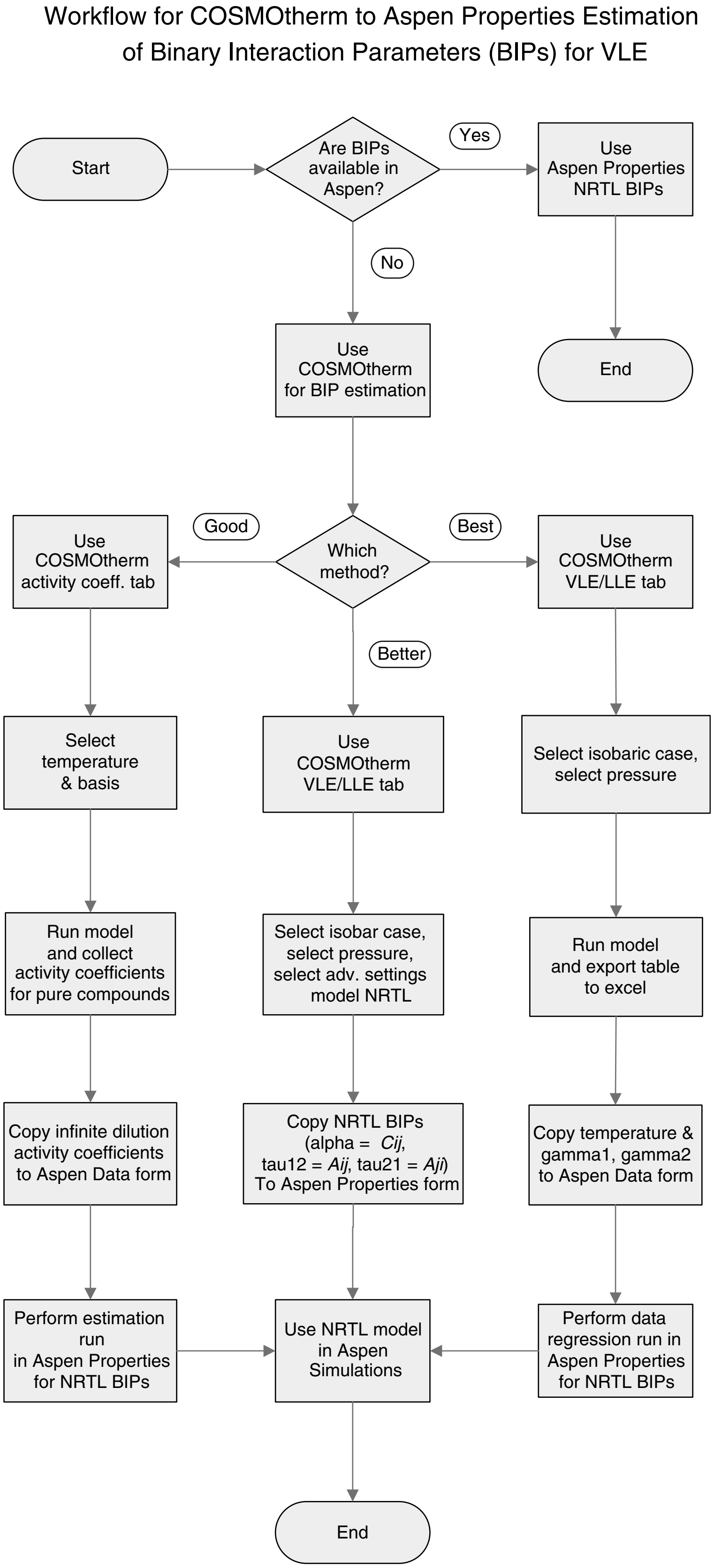
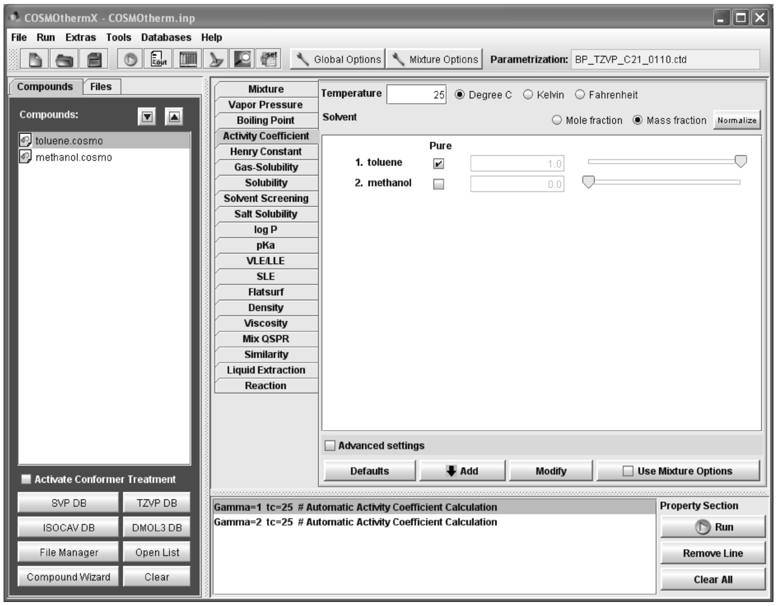


FIGURE 12.9 Binary interaction parameter estimation workflow.



Parametrization: BP_TZVP_C21_0110.ctd

toluene.cosmo
methanol.cosmo

Temperature 25 ● Degree C ○ Kelvin ○ Fahrenheit

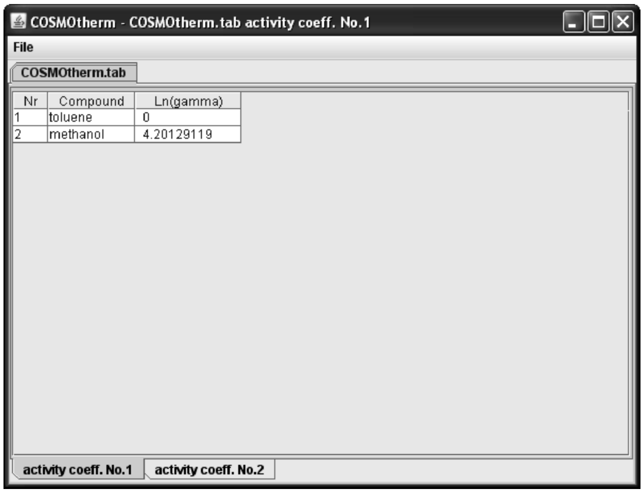
Solvent ○ Mole fraction ● Mass fraction

1. toluene ☑ 1.0
2. methanol ☐ 0.0

```
Gamma=1  tc=25  # Automatic Activity Coefficient Calculation
Gamma=2  tc=25  # Automatic Activity Coefficient Calculation
```

FIGURE 12.10 COSMOthermX activity coefficient user interface.

6. In the Aspen "Properties\Data" folder, create a data entry case.
7. Select "Mixture" as the Data type.
8. In the "Setup" tab, choose Category "For Estimation" and Data type "GAMINF", and then choose the pair of components for estimation.
9. Paste the temperature and gamma values in the appropriate locations on the "Data" tab (Figure 12.12).
10. In Aspen, select Tools/Estimation, and then request an estimation run within the Estimation folder.
11. Choose to "Estimate only the selected parameters."
12. On the Binary tab, specify Parameter "NRTL" and Method "Data" for "Component i" and "Component j" equal to "All."



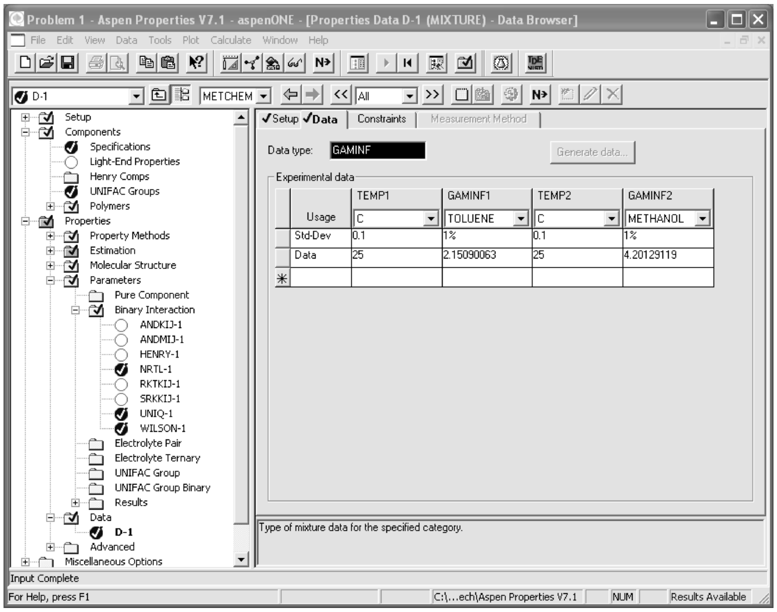
Nr	Compound	Ln(gamma)
1	toluene	0
2	methanol	4.20129119

FIGURE 12.11 COSMOthermX activity coefficient output.

13. Run the estimation and examine the results in the "Parameters\Binary Parameters\NRTL-1" folder. Source should read "R-PCES," which is "Regression Property Constant Estimation System" (Figure 12.13).
14. The NRTL BIPs are in place and are ready for use in process modeling.
15. *Caution*: The BIPs are a result from an *isothermal* estimation of *infinite dilution* activity coefficients in COSMOthermX. The range of applicability is relatively narrow.

Estimation of Isothermal NRTL BIPs through COSMOthermX for export to Aspen

1. Choose the VLE/LLE tab in COSMOthermX (Figure 12.14).
2. Select an Isothermal or Isobar case and set the appropriate conditions.
3. Choose the components and make note of the order of entry.
4. Check "Advanced settings" and "Compute empirical activity coefficient models?" and select the "NRTL" model.
5. Add the case and press "Run" to perform the estimation.
6. Examine the bottom section of the text output from the run (Figure 12.15).
7. NRTL rms is an indication of parameter fit.
8. Copy each of Alpha, Tau12, and Tau21.
9. Within Aspen, under the "Properties\Parameters\Binary Interaction\NRTL-1," paste the values from



Problem 1 - Aspen Properties V7.1 - aspenONE - [Properties Data D-1 (MIXTURE) - Data Browser]

Data type: GAMINF

Experimental data

	TEMP1	GAMINF1	TEMP2	GAMINF2
Usage	C	TOLUENE	C	METHANOL
Std-Dev	0.1	1%	0.1	1%
Data	25	2.15090063	25	4.20129119
✳				

Type of mixture data for the specified category.

Input Complete

FIGURE 12.12 Aspen Properties activity coefficient data input.

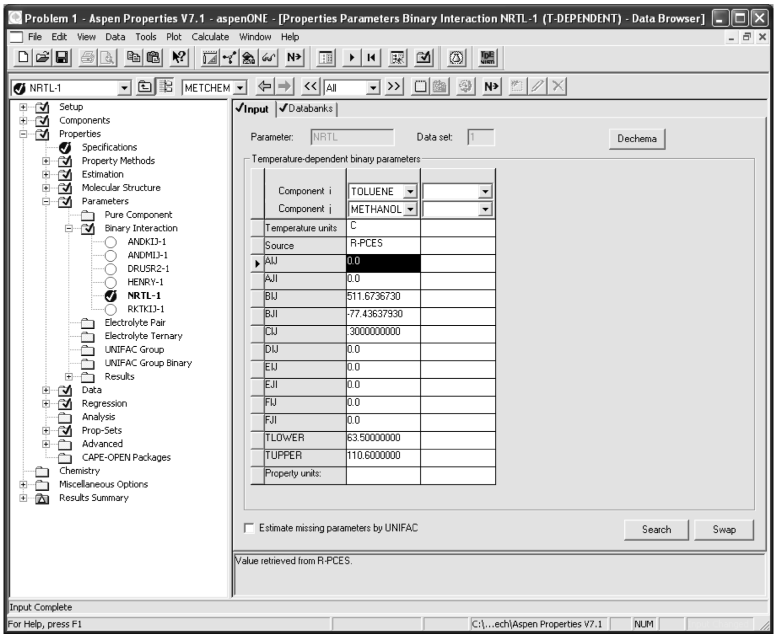
COSMOthermX NRTL BIPs as follows in the column labeled with the solvent pair (Figure 12.16):

(a) CIJ = NRTL Alpha

(b) AIJ = NRTL Tau12

(c) AJI = NRTL Tau21

10. After pasting the parameters, the Source should be "USER."
11. The NRTL BIPs are in place and are ready for use in process modeling.
12. *Caution*: The resulting BIPs are *isothermal* parameters from COSMOthermX. The range of applicability is somewhat narrow since the parameters do not include coefficients for temperature-dependent NRTL terms.



Problem 1 - Aspen Properties V7.1 - aspenONE - [Properties Parameters Binary Interaction NRTL-1 (T-DEPENDENT) - Data Browser]

Parameter: NRTL Data set: 1

Temperature-dependent binary parameters

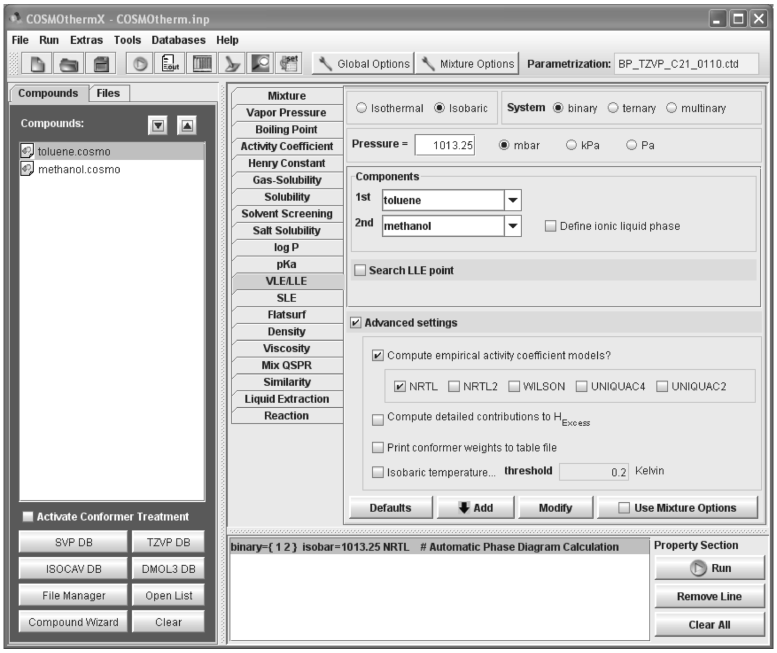
Component i	TOLUENE	
Component j	METHANOL	
Temperature units	C	
Source	R-PCES	
AIJ	0.0	
AJI	0.0	
BIJ	511.6736730	
BJI	-77.43637930	
CIJ	.3000000000	
DIJ	0.0	
EIJ	0.0	
EJI	0.0	
FIJ	0.0	
FJI	0.0	
TLOWER	63.50000000	
TUPPER	110.6000000	
Property units:		

☐ Estimate missing parameters by UNIFAC

Value retrieved from R-PCES.

Input Complete

FIGURE 12.13 Aspen Properties estimated NRTL binary parameters.



Parametrization: BP_TZVP_C21_0110.ctd

toluene.cosmo
methanol.cosmo

○ Isothermal ● Isobaric

System ● binary ○ ternary ○ multinary

Pressure = 1013.25 ● mbar ○ kPa ○ Pa

Components
1st toluene
2nd methanol
☐ Define ionic liquid phase

☐ Search LLE point

☑ Advanced settings

☑ Compute empirical activity coefficient models?

☑ NRTL ☐ NRTL2 ☐ WILSON ☐ UNIQUAC4 ☐ UNIQUAC2

☐ Compute detailed contributions to H_{Excess}

☐ Print conformer weights to table file

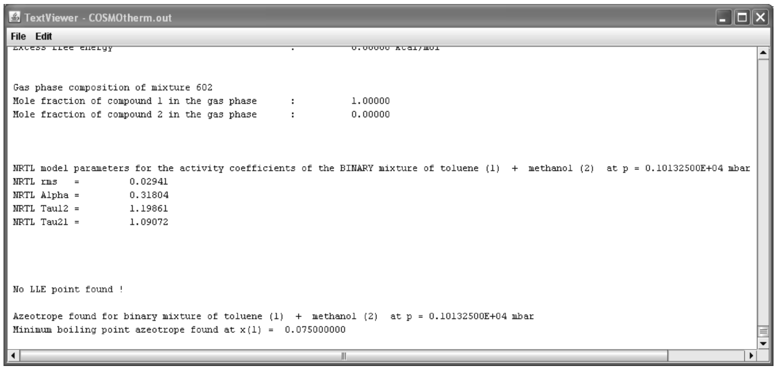
☐ Isobaric temperature... threshold 0.2 Kelvin

```
binary={ 1 2 } isobar=1013.25 NRTL   # Automatic Phase Diagram Calculation
```

FIGURE 12.14 COSMOthermX VLE/LLE user interface for NRTL binary parameter estimation.

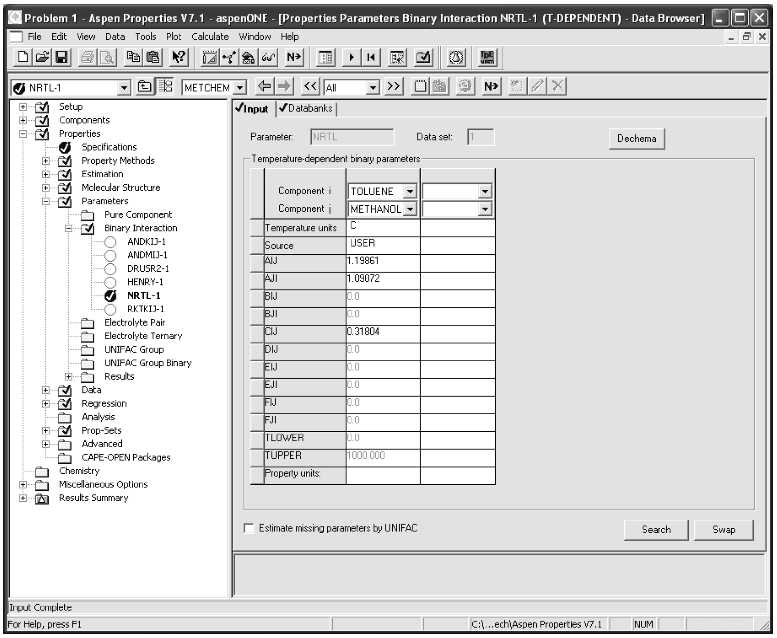
Estimation of NRTL BIPs from COSMOthermX liquid activity coefficients

1. In COSMOthermX, select the VLE/LLE tab (Figure 12.17).
2. Select an Isothermal or Isobar case and set the appropriate conditions.
3. Choose the components and make note of the order of entry.
4. Select "Search LLE point" with "default grid" algorithm.
5. Add the case and "Run" to perform the estimation.
6. Examine the tabular output from the run (Figure 12.18).
7. Choose "File\Save As" and save the file to a convenient location with a desirable filename.
8. In the Excel spreadsheet, insert columns after ln(γ1) and ln(γ2) as shown in Figure 12.19.
9. In the new columns, calculate "gamma1" and "gamma2" as exp(ln(γ)) for each (Figure 12.19).
10. In the Aspen "Properties\Data" folder, create a data entry case for a mixture.
11. In the "Setup" tab, choose Category "Thermodynamic" and Data type "GAMMA," and choose the



```
Excess free energy                                :          0.00000 kcal/mol


Gas phase composition of mixture 602
Mole fraction of compound 1 in the gas phase      :          1.00000
Mole fraction of compound 2 in the gas phase      :          0.00000




NRTL model parameters for the activity coefficients of the BINARY mixture of toluene (1)  +  methanol (2)  at p = 0.10132500E+04 mbar
NRTL rms   =         0.02941
NRTL Alpha =         0.31804
NRTL Tau12 =         1.19861
NRTL Tau21 =         1.09072




No LLE point found !

Azeotrope found for binary mixture of toluene (1)  +  methanol (2)  at p = 0.10132500E+04 mbar
Minimum boiling point azeotrope found at x(1) =  0.075000000
```

FIGURE 12.15 COSMOthermX NRTL binary parameter output.



Parameter: NRTL Data set: 1

Temperature-dependent binary parameters

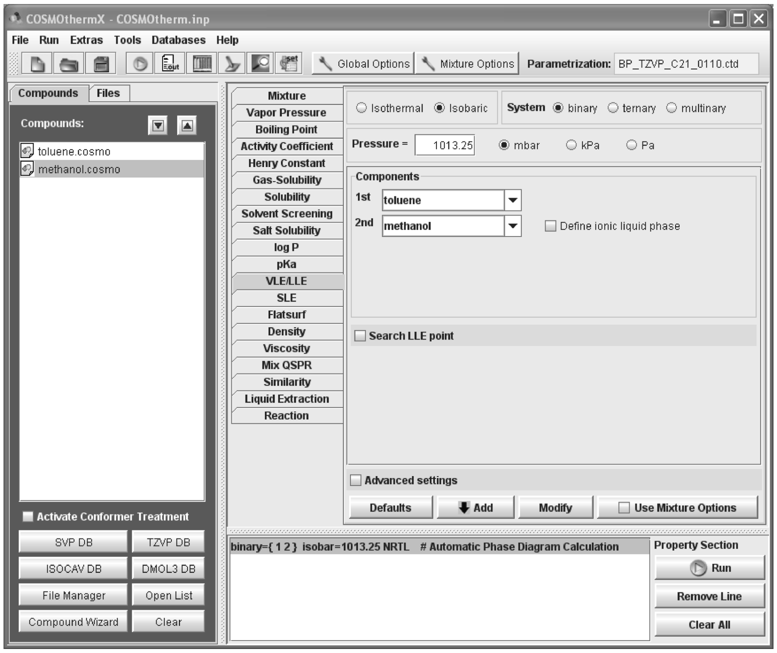
Component i	TOLUENE	
Component j	METHANOL	
Temperature units	C	
Source	USER	
AIJ	1.19861	
AJI	1.09072	
BIJ	0.0	
BJI	0.0	
CIJ	0.31804	
DIJ	0.0	
EIJ	0.0	
EJI	0.0	
FIJ	0.0	
FJI	0.0	
TLOWER	0.0	
TUPPER	1000.000	
Property units:		

☐ Estimate missing parameters by UNIFAC

FIGURE 12.16 Aspen Properties NRTL binary parameter user input.

binary pair for estimation. Set the pressure at the bottom to that of the system.

12. Paste the temperatures and gamma values in the appropriate locations (Figure 12.20).
13. In Aspen, choose Tools\Regression, and then start a new case in the Regression folder. Choose the name of Data Set in the "Setup" section of Regression.
14. Under the Parameters tab, choose "Binary parameter" for type, select the Name as NRTL, and set Elements 1, 2, and 3 as shown in Figure 12.21.
15. For components, select the pair used in the COSMOthermX estimation.
16. Repeat the component pair for the same element but in reverse order, except for Element 3, which is



Parametrization: BP_TZVP_C21_0110.ctd

Compounds: toluene.cosmo, methanol.cosmo

○ Isothermal ● Isobaric System ● binary ○ ternary ○ multinary

Pressure = 1013.25 ● mbar ○ kPa ○ Pa

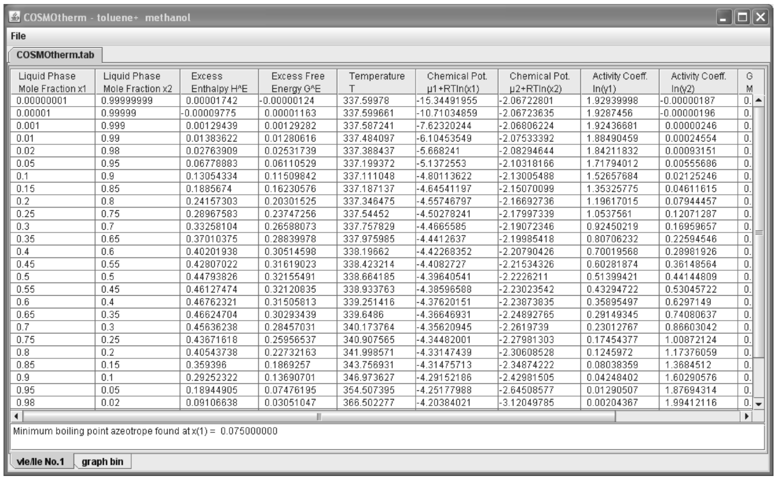
Components
1st toluene
2nd methanol
☐ Define ionic liquid phase

☐ Search LLE point

☐ Advanced settings

```
binary={ 1 2 } isobar=1013.25 NRTL   # Automatic Phase Diagram Calculation
```

FIGURE 12.17 COSMOthermX VLE/LLE user interface for data estimation.



Liquid Phase Mole Fraction x1	Liquid Phase Mole Fraction x2	Excess Enthalpy H^E	Excess Free Energy G^E	Temperature T	Chemical Pot. μ1+RTln(x1)	Chemical Pot. μ2+RTln(x2)	Activity Coeff. ln(γ1)	Activity Coeff. ln(γ2)	G M
0.00000001	0.99999999	0.00001742	-0.00000124	337.59978	-15.34491955	-2.06722801	1.92939998	-0.00000187	0.
0.00001	0.99999	-0.00009775	0.00001163	337.599661	-10.71034859	-2.06723635	1.9287456	-0.00000196	0.
0.001	0.999	0.00129439	0.00129282	337.587241	-7.62320244	-2.06806224	1.92436681	0.00000246	0.
0.01	0.99	0.01383622	0.01280616	337.484097	-6.10453549	-2.07533392	1.88490459	0.00024554	0.
0.02	0.98	0.02763909	0.02531739	337.388437	-5.668241	-2.08294644	1.84211832	0.00093151	0.
0.05	0.95	0.06778883	0.06110529	337.199372	-5.1372553	-2.10318166	1.71794012	0.00555686	0.
0.1	0.9	0.13054334	0.11509842	337.111048	-4.80113622	-2.13005488	1.52657684	0.02125246	0.
0.15	0.85	0.1885674	0.16230576	337.187137	-4.64541197	-2.15070099	1.35325775	0.04611615	0.
0.2	0.8	0.24157303	0.20301525	337.346475	-4.55746797	-2.16692736	1.19617015	0.07944457	0.
0.25	0.75	0.28967583	0.23747256	337.54452	-4.50278241	-2.17997339	1.0537561	0.12071287	0.
0.3	0.7	0.33258104	0.26588073	337.757829	-4.4665585	-2.19072346	0.92450219	0.16959657	0.
0.35	0.65	0.37010375	0.28839978	337.975985	-4.4412637	-2.19985418	0.80706232	0.22594546	0.
0.4	0.6	0.40201938	0.30514598	338.19662	-4.42268352	-2.20790426	0.70019568	0.28981926	0.
0.45	0.55	0.42807022	0.31619023	338.423214	-4.4082727	-2.21534326	0.60281874	0.36148564	0.
0.5	0.5	0.44793826	0.32155491	338.664185	-4.39640541	-2.2226211	0.51399421	0.44144809	0.
0.55	0.45	0.46127474	0.32120835	338.933763	-4.38596588	-2.23023542	0.43294722	0.53045722	0.
0.6	0.4	0.46762321	0.31505813	339.251416	-4.37620151	-2.23873835	0.35895497	0.6297149	0.
0.65	0.35	0.46624704	0.30293439	339.6486	-4.36646931	-2.24892765	0.29149345	0.74080637	0.
0.7	0.3	0.45636238	0.28457031	340.173764	-4.35620945	-2.2619739	0.23012767	0.86603042	0.
0.75	0.25	0.43671618	0.25956537	340.907565	-4.34482001	-2.27981303	0.17454377	1.00872124	0.
0.8	0.2	0.40543738	0.22732163	341.998571	-4.33147439	-2.30608528	0.1245972	1.17376059	0.
0.85	0.15	0.359396	0.1869257	343.756931	-4.31475713	-2.34874222	0.08038359	1.3684512	0.
0.9	0.1	0.29252322	0.13690701	346.973627	-4.29152186	-2.42981505	0.04248402	1.60290576	0.
0.95	0.05	0.18944905	0.07476195	354.507395	-4.25177988	-2.64508577	0.01290507	1.87694314	0.
0.98	0.02	0.09106638	0.03051047	366.502277	-4.20384021	-3.12049785	0.00204367	1.99412116	0.

Minimum boiling point azeotrope found at x(1) = 0.075000000

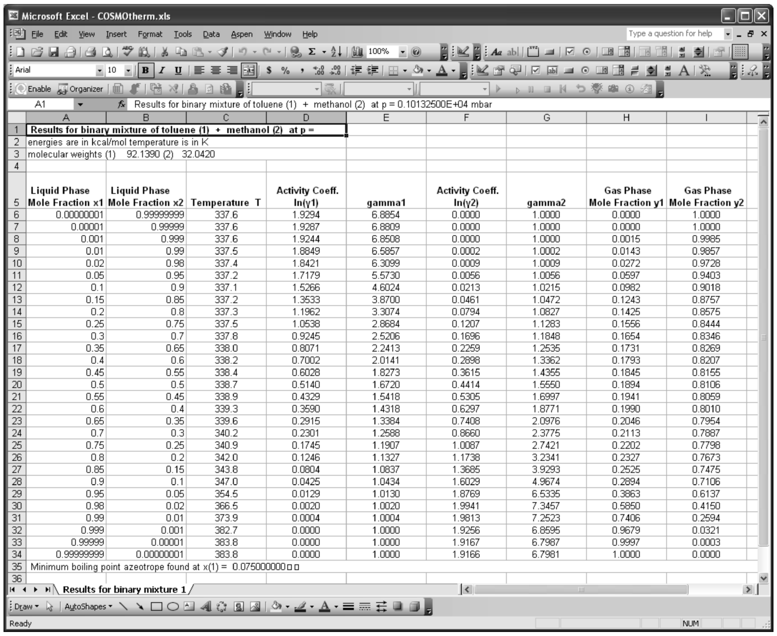
FIGURE 12.18 COSMOthermX VLE data output.

symmetric and only has one value. Optionally, "fix" the value of Element 3 under the "Usage" option.

17. Run the regression and examine the results under the Regression folder for closeness of fit. Predicted versus entered data can be plotted in the same area.
18. Examine the results in the "Parameters\Binary Parameters\NRTL-1" folder. Source should read "R-R-#," which means a result from regression case (Figure 12.22).
19. The NRTL BIPs are in place and are ready for use in process modeling.
20. *Caution*: The BIPs are a result of a regression across the boiling point temperature range of the liquid pair (i.e., an isobar case), which defines the range of applicability. To obtain NRTL BIPs at a different pressure, either *extend the first data set* by running a new case in COSMOthermX at a different isobaric condition, *or create a separate Regression case* in Aspen for the additional COSMOthermX isobaric data.

Examining the quality of liquid activity coefficients after estimation or regression

1. In Aspen, view the NRTL BIPs in the "Parameters \Binary Parameters\NRTL-1" folder and select the appropriate "Source."



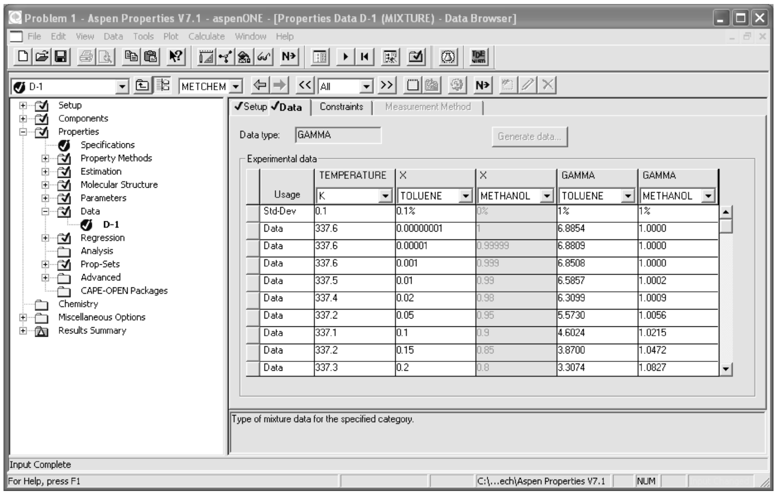
A1: Results for binary mixture of toluene (1) + methanol (2) at p = 0.10132500E+04 mbar

1 **Results for binary mixture of toluene (1) + methanol (2) at p =**
2 energies are in kcal/mol temperature is in K
3 molecular weights (1) 92.1390 (2) 32.0420
4

	A	B	C	D	E	F	G	H	I
5	**Liquid Phase Mole Fraction x1**	**Liquid Phase Mole Fraction x2**	**Temperature T**	**Activity Coeff. ln(γ1)**	**gamma1**	**Activity Coeff. ln(γ2)**	**gamma2**	**Gas Phase Mole Fraction y1**	**Gas Phase Mole Fraction y2**
6	0.00000001	0.99999999	337.6	1.9294	6.8854	0.0000	1.0000	0.0000	1.0000
7	0.00001	0.99999	337.6	1.9287	6.8809	0.0000	1.0000	0.0000	1.0000
8	0.001	0.999	337.6	1.9244	6.8508	0.0000	1.0000	0.0015	0.9985
9	0.01	0.99	337.5	1.8849	6.5857	0.0002	1.0002	0.0143	0.9857
10	0.02	0.98	337.4	1.8421	6.3099	0.0009	1.0009	0.0272	0.9728
11	0.05	0.95	337.2	1.7179	5.5730	0.0056	1.0056	0.0597	0.9403
12	0.1	0.9	337.1	1.5266	4.6024	0.0213	1.0215	0.0982	0.9018
13	0.15	0.85	337.2	1.3533	3.8700	0.0461	1.0472	0.1243	0.8757
14	0.2	0.8	337.3	1.1962	3.3074	0.0794	1.0827	0.1425	0.8575
15	0.25	0.75	337.5	1.0538	2.8684	0.1207	1.1283	0.1556	0.8444
16	0.3	0.7	337.8	0.9245	2.5206	0.1696	1.1848	0.1654	0.8346
17	0.35	0.65	338.0	0.8071	2.2413	0.2259	1.2535	0.1731	0.8269
18	0.4	0.6	338.2	0.7002	2.0141	0.2898	1.3362	0.1793	0.8207
19	0.45	0.55	338.4	0.6028	1.8273	0.3615	1.4355	0.1845	0.8155
20	0.5	0.5	338.7	0.5140	1.6720	0.4414	1.5550	0.1894	0.8106
21	0.55	0.45	338.9	0.4329	1.5418	0.5305	1.6997	0.1941	0.8059
22	0.6	0.4	339.3	0.3590	1.4318	0.6297	1.8771	0.1990	0.8010
23	0.65	0.35	339.6	0.2915	1.3384	0.7408	2.0976	0.2046	0.7954
24	0.7	0.3	340.2	0.2301	1.2588	0.8660	2.3775	0.2113	0.7887
25	0.75	0.25	340.9	0.1745	1.1907	1.0087	2.7421	0.2202	0.7798
26	0.8	0.2	342.0	0.1246	1.1327	1.1738	3.2341	0.2327	0.7673
27	0.85	0.15	343.8	0.0804	1.0837	1.3685	3.9293	0.2525	0.7475
28	0.9	0.1	347.0	0.0425	1.0434	1.6029	4.9674	0.2894	0.7106
29	0.95	0.05	354.5	0.0129	1.0130	1.8769	6.5335	0.3863	0.6137
30	0.98	0.02	366.5	0.0020	1.0020	1.9941	7.3457	0.5850	0.4150
31	0.99	0.01	373.9	0.0004	1.0004	1.9813	7.2523	0.7406	0.2594
32	0.999	0.001	382.7	0.0000	1.0000	1.9256	6.8595	0.9679	0.0321
33	0.99999	0.00001	383.8	0.0000	1.0000	1.9167	6.7987	0.9997	0.0003
34	0.99999999	0.00000001	383.8	0.0000	1.0000	1.9166	6.7981	1.0000	0.0000

35 Minimum boiling point azeotrope found at x(1) = 0.075000000□□
36

FIGURE 12.19 COSMOthermX VLE data exported to Microsoft Excel.



Problem 1 - Aspen Properties V7.1 - aspenONE - [Properties Data D-1 (MIXTURE) - Data Browser]

Data type: GAMMA

Experimental data

	TEMPERATURE	X	X	GAMMA	GAMMA
Usage	K	TOLUENE	METHANOL	TOLUENE	METHANOL
Std-Dev	0.1	0.1%	0%	1%	1%
Data	337.6	0.00000001	1	6.8854	1.0000
Data	337.6	0.00001	0.99999	6.8809	1.0000
Data	337.6	0.001	0.999	6.8508	1.0000
Data	337.5	0.01	0.99	6.5857	1.0002
Data	337.4	0.02	0.98	6.3099	1.0009
Data	337.2	0.05	0.95	5.5730	1.0056
Data	337.1	0.1	0.9	4.6024	1.0215
Data	337.2	0.15	0.85	3.8700	1.0472
Data	337.3	0.2	0.8	3.3074	1.0827

Type of mixture data for the specified category.

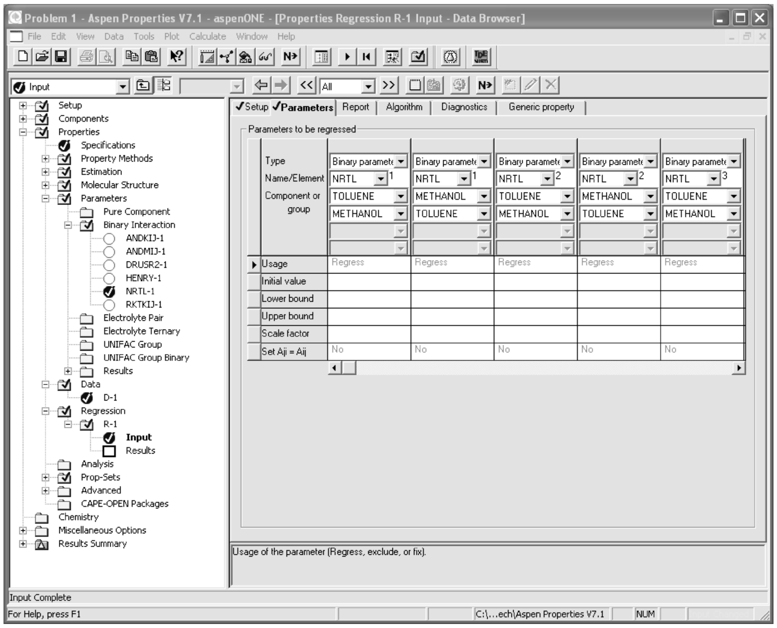
Input Complete

FIGURE 12.20 Aspen Properties user interface for VLE data input.

2. Under "Tools\Analysis\Binary," choose Type *T-xy* or *P-xy*, set other conditions to match those of the regressed or estimated BIPs, then run the analysis.
3. After seeing the resulting phase diagram, close the plot and choose the "Plot Wizard" from the table that appears.
4. In the Plot Wizard, choose "Gammas" as the desired plot.
5. An example of the resulting plot of liquid activity coefficients for each component is shown (Figure 12.23).

Comparison of T-xy diagrams and liquid activity coefficients by source

A graphical comparison of VLE and liquid activity coefficient data retrieved from various Aspen Properties data banks and generated through COSMOthermX is shown in Figures 12.24–12.29. Three pairs of binary systems is considered in these examples: (1) the zeotropic system of methanol and water (Figures 12.24 and 12.25), (2) the minimum boiling, homogeneous azeotropic system of acetonitrile and isopropanol (Figures 12.26 and 12.27), and (3) the minimum boiling, heterogeneous azeotropic system



Problem 1 - Aspen Properties V7.1 - aspenONE - [Properties Regression R-1 Input - Data Browser]

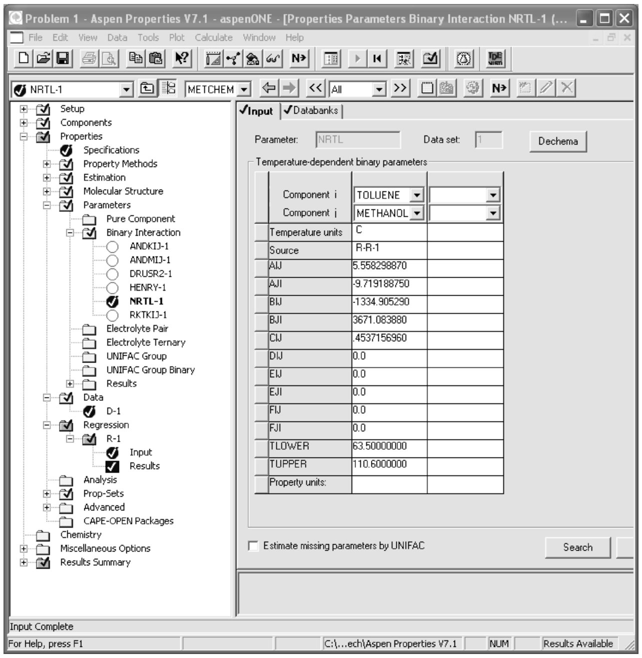
Parameters to be regressed

Type	Binary paramete	Binary paramete	Binary paramete	Binary paramete	Binary paramete
Name/Element	NRTL 1	NRTL 1	NRTL 2	NRTL 2	NRTL 3
Component or group	TOLUENE METHANOL	METHANOL TOLUENE	TOLUENE METHANOL	METHANOL TOLUENE	TOLUENE METHANOL
Usage	Regress	Regress	Regress	Regress	Regress
Initial value					
Lower bound					
Upper bound					
Scale factor					
Set Aji = Aij	No	No	No	No	No

Usage of the parameter (Regress, exclude, or fix).

Input Complete

FIGURE 12.21 Aspen Properties data regression user interface.



Parameter: NRTL Data set: 1

Temperature-dependent binary parameters

Component i	TOLUENE	
Component j	METHANOL	
Temperature units	C	
Source	R-R-1	
AIJ	5.558298870	
AJI	-9.719188750	
BIJ	-1334.905290	
BJI	3671.083880	
CIJ	.4537156960	
DIJ	0.0	
EIJ	0.0	
EJI	0.0	
FIJ	0.0	
FJI	0.0	
TLOWER	63.50000000	
TUPPER	110.6000000	
Property units:		

☐ Estimate missing parameters by UNIFAC

FIGURE 12.22 Aspen Properties VLE data regression results.

of *n*-butanol and water (Figures 12.28 and 12.29). In each case, the *T-xy* phase diagrams and liquid-phase activity coefficients plots were generated with the aid of COSMOthermX using the infinite dilution, NRTL parameter, and gamma regression protocols described in this guide. These three cases demonstrate that COSMOthermX is an exceptional method of obtaining estimated VLE data, and associated binary interaction parameter data, in the

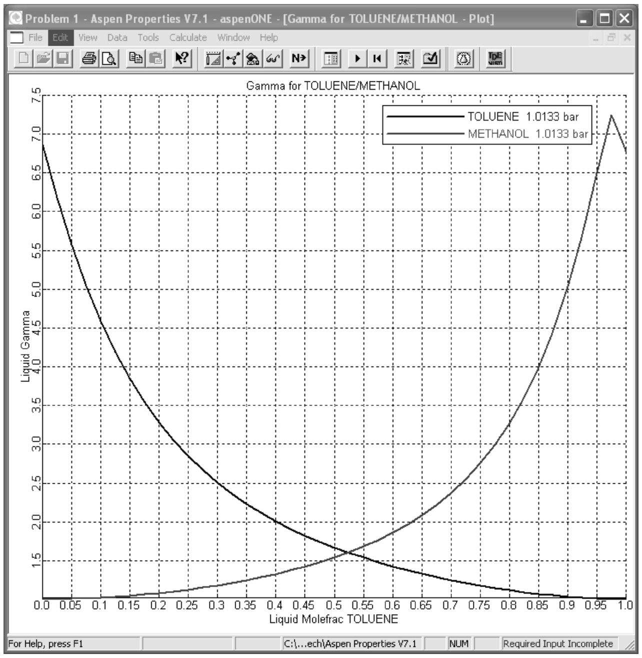


FIGURE 12.23 Aspen Properties plot of binary activity coefficients.

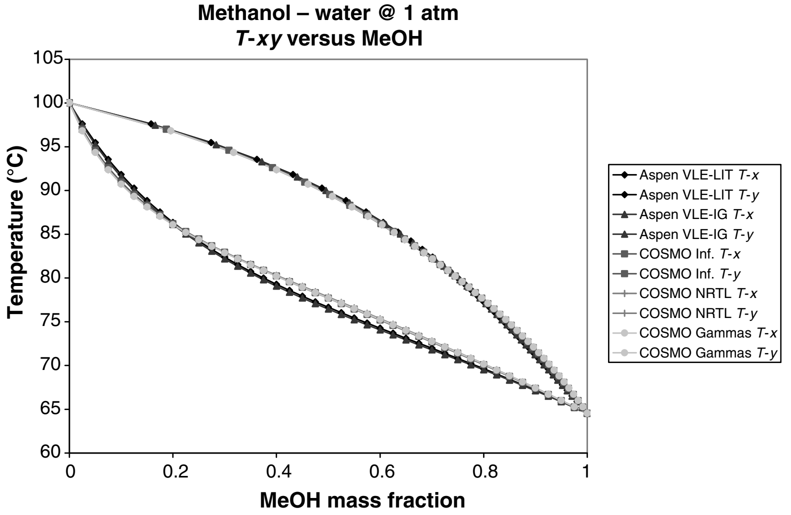


FIGURE 12.24 Comparison of Aspen Data bank and COSMOthermX data for *T-xy* phase diagram for methanol and water at 1 atm.

absence of laboratory or literature data. Aspen Properties is a convenient platform for the collection and regression of equilibrium data for further use in process modeling. The COSMOthermX estimation method provides immediate answers about the potential of azeotropic behavior, mixture boiling points, and relative volatility. As with any estimation technique, some deviation from real properties is expected, but the degree of deviation varies depending on the system. For these three cases, the deviations are not significant in all three categories of estimation. The results are plotted against two sources of Aspen Properties data bank data: VLE-IG (Dortmund Data Bank with ideal gas EOS) and VLE-LIT (other literature values including Dortmund Data Bank with ideal gas EOS). The three COSMOthermX estimation protocols are represented in the plots by this nomenclature: (1) "COSMO Inf" for estimation with infinite dilution activity coefficients, (2) "COSMO NRTL" for estimation from COSMOthermX generated NRTL binary parameters, and (3) "COSMO Gammas" for the regression of COSMOthermX liquid activity coefficient data within Aspen Properties. Generally, the COSMOthermX derived results are tightly grouped

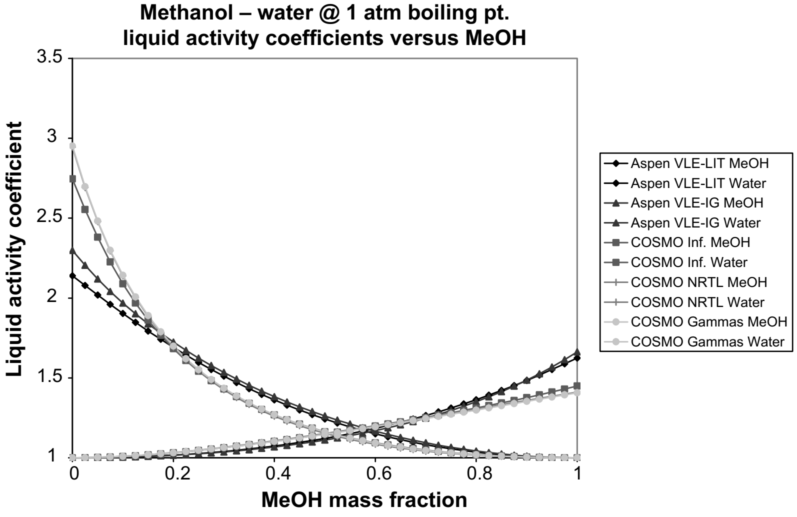


FIGURE 12.25 Comparison of Aspen Data bank and COSMOthermX data for liquid-phase activity coefficients for methanol and water at 1 atm.

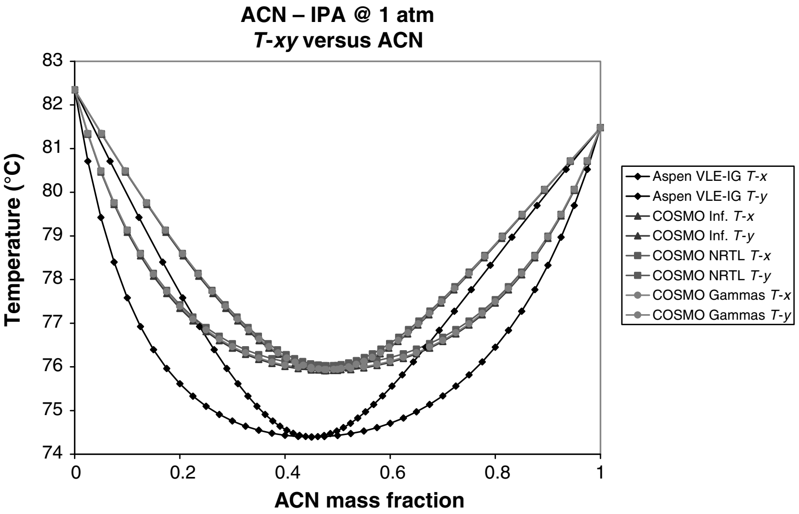


FIGURE 12.26 Comparison of Aspen Data bank and COSMOthermX data for *T-xy* phase diagram for acetonitrile and isopropanol at 1 atm with a homogeneous minimum boiling azeotrope.

in the resulting plots and in all cases the prediction of zeotropic and azeotropic behavior matches that from the Aspen Properties data banks. For the azeotropic systems, the boiling points of the mixtures deviates by less than 2°C and the composition of the binary azeotrope is offset by less than 0.1 mass fraction units. The activity coefficient plots show the greatest deviation from the data bank values at the end points approaching infinite dilution, although this deviation does not impact the *T-xy* phase diagram results to any great degree. As interest in any particular pair of components increases, the accuracy of the underlying physical properties can be improved with data from other sources and Aspen Properties can be used as a continuing storage and regression point for the information. COSMOthermX estimation techniques for binary interaction parameters have been used to successfully create custom data banks in Aspen Properties for thousands of binary systems not initially available from Aspen Properties data banks.

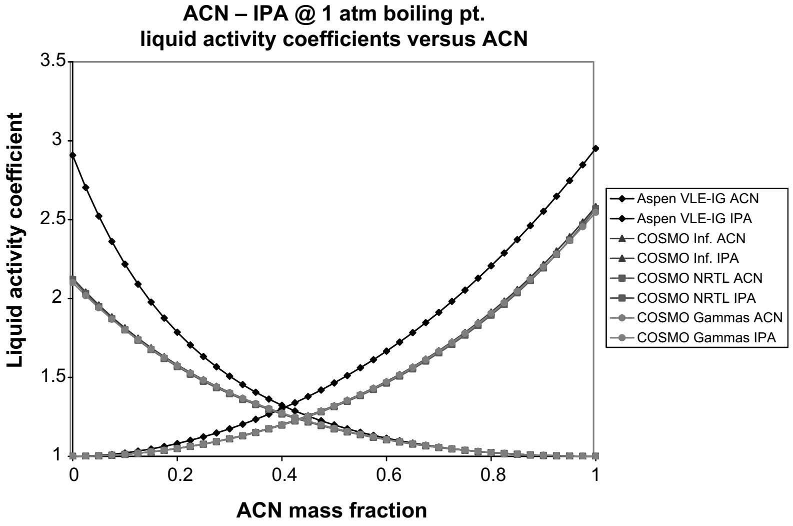


FIGURE 12.27 Comparison of Aspen Data bank and COSMOthermX data for liquid-phase activity coefficients for acetonitrile and isopropanol at 1 atm.

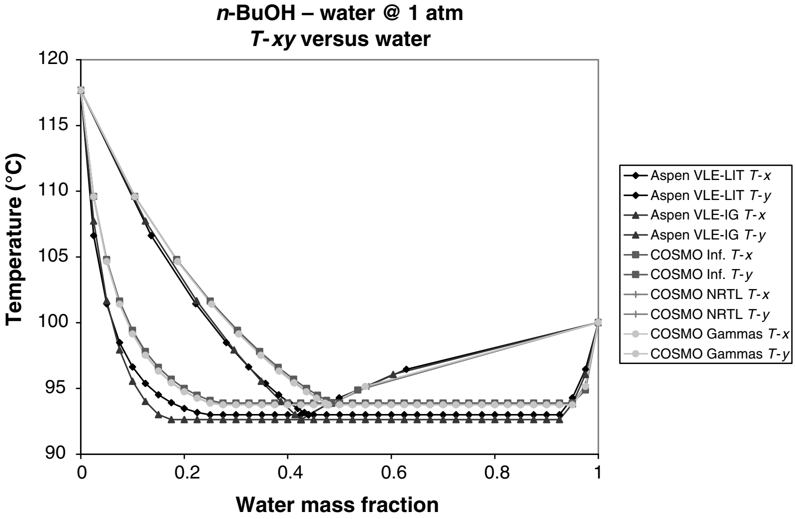


FIGURE 12.28 Comparison of Aspen Data bank and COSMOthermX data for *T-xy* phase diagram for *n*-butanol and water at 1 atm with a heterogeneous minimum boiling azeotrope.

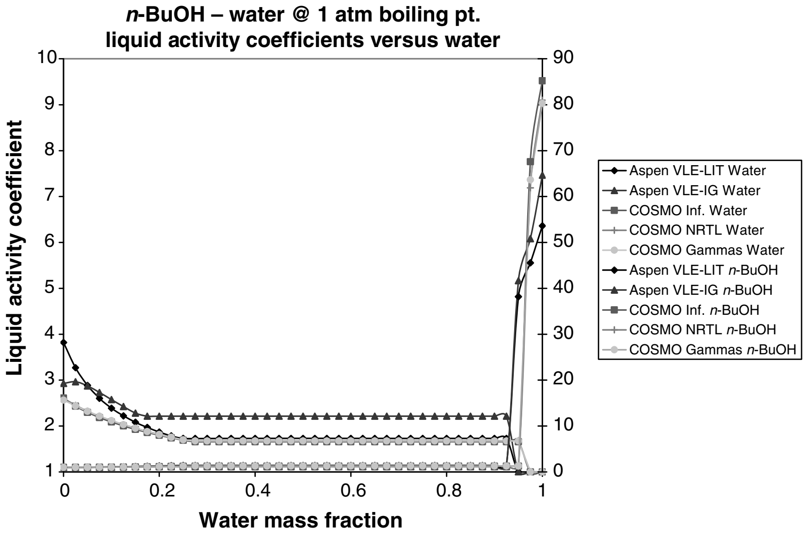


FIGURE 12.29 Comparison of Aspen Data bank and COSMOthermX data for liquid-phase activity coefficients for methanol and water at 1 atm.

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