Applications of Process Thermodynamics in Pharmaceutical Coating

Michael Choi
PCTS, Inc., Montgomeryville, PA

Abstract

The utility of process thermodynamics analysis in solving spray coating problems were explored in this article. Case study examples included the analysis of a coating process, scale up and optimization, troubleshooting of a manufacturing process, development of a solvent formulation, design of process control limits, and design of experiments. To establish the relationship between the process thermodynamics variables and process control variables for these case studies, the steady-state material and energy balance equations were introduced. However, the analysis of the variables in the equations pointed to the fact that additional information was needed to solve these equations. Experimental investigation of heat loss revealed that the heat loss remained relatively constant if the process did not change drastically. Using this finding, the utility of the process thermodynamics could be shown through these case studies. Since process thermodynamics relationship is the same for any spray coating process as well as spray drying process, the examples provided in this article can be applied to pan, Wurster, fluid bed coaters, spray dryers, and any other spray systems.

The role of process thermodynamics in the coating process was also examined using mass transfer rate equations. The analysis showed that process thermodynamics may be very important for the control of the drying rate at low spray rate and low weight gain. However, at high spray rate and large weight gain, the coating solution formulation may control the drying rate.
Introduction

The term “thermodynamics” was popularized by Ebey\textsuperscript{1} in the late 1980’s to describe the steady-state environment in which the spray coating takes place. This term at the time was convenient since one of the equations describing the environmental condition was based on the first law of thermodynamics\textsuperscript{2}, which states that energy is conserved within a given system. However, a quick examination of the spray coating process reveals that the coating process involves much more thermodynamics than the first law of thermodynamics. For example, in spray coating processes, coating solution is atomized into fine droplets as it exits from a nozzle, usually assisted by the atomizing air and into a specific pattern by the fan air. The spray droplets travel a short distance from the nozzle to the target (tablet, pellets, granules, and powder) surface. As the droplets impinge on the target, the droplets wet and spread on the surface of the target, thereby forming a film as the droplet coalesces and adhere to the target surface. Of these steps, the initial distribution and size of the droplets may be the only step that thermodynamics is of little importance. All other steps involve drying of the coating substrate in air and on target surface where thermodynamics other than the first law of thermodynamics also play an important role. The environmental condition relationship derived from the first law of thermodynamics is herein referred to as the “process thermodynamics” to distinguish it from the general thermodynamics describing the coating process.

Another limitation of process thermodynamics is that the material and energy balances used to derive the relationship for the environmental conditioning factors is for steady-state conditions. Steady-state is achieved usually in 15 minutes or longer into the coating process for typical commercial-scale coating processes. Therefore, application of process thermodynamics is limited to conditions after the steady state is reached.

Despite these limitations, the process thermodynamics characterization has many uses. Many manufacturing troubleshooting problems relate to instrument failures, which can be pinpointed quickly through the analysis of process thermodynamics. Scale up and tech transfers can be greatly simplified by bridging processes at environmentally equivalent conditions. Product formulation can be done with manufacturing capacity considerations using process thermodynamics relationship, and designs of experiments can be done using critical process thermodynamics variables that may not be independent variables.

The main purpose of this article is to highlight the utility of process thermodynamics in the pharmaceutical industry through case studies. In doing this, the relationship between process thermodynamics variables and process control variables needed to be derived first to explain the utilization of process thermodynamics relationship. The importance of process heat loss is also explored as this is key information that is needed to complete the process thermodynamics characterization. To illustrate the limitation of process thermodynamics in describing the coating process, the relationship between the material, atomization, transport, and thermodynamics properties was derived through the analysis of mass transfer rates.
Note that the definition of “environmental condition” or “process thermodynamics” used in this article is defined by the bulk bed temperature, pressure, and vapor content. However, since most coating processes in the pharmaceutical industry are open processes operating close to the atmospheric pressure, the environmental condition refers to the bed temperature and humidity. Also, no attempt was made to cite recent developments in process thermodynamics in this article as this was provided recently by Ende and Berchielli³.

**Process Control Variables and Thermodynamics Variables**

The schematic for a coating process is shown in Figure 1. In most coating operations, the control of the coating process is done by manipulating the independent variables shown in Table 1. The system response, or dependent, variables are also shown in Table 1. The exhaust temperature and relative humidity are considered the “process thermodynamics” variables as these define the coating environment. In some coating operations, the exhaust temperature is controlled by manipulating the process air temperature. Only in rare operations, the humidity of the bed or exhaust is controlled.

The relationship between these independent and dependent variables can be derived from the analysis of the process. The material balance equation describing the gas phase of the coating process at steady state is given by

\[
\rho_{\text{exh}} Q_{\text{exh}} = \rho_{\text{at}} (Q_{\text{at}} + Q_{\text{fan}}) + \rho_{\text{in}} Q_{\text{in}} + W_{\text{sp}} (1 - x_s)
\]  

(1)

Material balance around the solvent component \(a\) is given by

\[
\rho_{\text{exh}} Q_{\text{exh}} y_{a,\text{exh}} = \rho_{\text{at}} (Q_{\text{at}} + Q_{\text{fan}})(y_{a,\text{at}}) + \rho_{\text{in}} Q_{\text{in}} (y_{a,\text{in}}) + W_{\text{sp}} (x_a)(1 - x_s)
\]

(2)

This equation applies to each component in the solvent—for example, if three components are in the solvent, three equations describe each component. The steady-state energy balance is given by

\[
Q_{\text{int}} \int_{T_{\text{exh}}}^{T_{\text{at}}} C_{p,\text{at}} dT = \Delta H_{\text{loss}} + (Q_{\text{at}} + Q_{\text{fan}}) \rho_{\text{at}} \int_{T_{\text{exh}}}^{T_{\text{at}}} C_{p,\text{at}} dT
\]

\[
+ W_{\text{sp}} (1 - x_s) \int_{T_{\text{exh}}}^{T_{\text{at}}} C_{p,\text{sol}} dT - W_{\text{sp}} (1 - x_s) \lambda_{\text{sol}}
\]

(3)

Exhaust relative humidity (RH\(_{a,\text{exh}}\)) is defined as

\[
\text{RH}_{a,\text{exh}} = \frac{P_{a,\text{exh}}}{P_{a,\text{exh}}^s} \frac{y_{a,\text{exh}} P}{P_{a,\text{exh}}^s}
\]

(4)

By definition, the moisture content in the process air is given by
Substituting Equations 4 and 5 into Equation 2 and assuming negligible moisture in the atomizing air results in the following relationship:

$$
\rho_{exh} Q_{exh} RH_{a,exh} \rho_{sat} = \rho_{inl} Q_{inl} \frac{p_{a,rel}}{P} + W_{sp} (x_a) (1 - x_s)
$$

Heat capacities ($C_{p,air}$ and $C_{p,sol}$), saturation vapor pressures ($p_{a,td}^{sat}$ and $p_{a,ext}^{sat}$), air densities ($\rho_{inl}$, $\rho_{at}$, and $\rho_{exh}$), and heat of vaporization ($\lambda_{sol}$) can be determined from equations of state based on temperature, pressure, and composition information. Equations 1, 3 and 6 still cannot be solved as there are twelve variables, three equations, and eight independent variables—leaving one degree of freedom. Another equation is needed to solve for the four dependent variables.

**Heat Loss**

A heat transfer equation describing the heat loss and experimental measurements of heat loss were considered to make up this additional equation needed to solve Equations 1, 3, and 6. The overall heat transfer equation describing the heat loss ($\Delta H_{loss}$) is given by (see, for example, Holman):

$$
\Delta H_{loss} = U_{inl} A_{inl} \Delta T_{LM, inl} + U_{exh} A_{exh} \Delta T_{LM, exh}
$$

where

$$
\Delta T_{LM, inl} = \frac{(T_{inl, 2} - T_r) - (T_{inl} - T_r)}{\log \left( \frac{T_{inl, 2} - T_r}{T_{inl} - T_r} \right)}
$$

$$
\Delta T_{LM, exh} = \frac{(T_{exh} - T_r) - (T_b - T_r)}{\log \left( \frac{T_{exh} - T_r}{T_b - T_r} \right)}
$$

$T_{inl}$, $T_{inl, 2}$, $T_{exh}$, $T_b$, and $T_r$ are temperatures of process air at the temperature probe, process air as it enters the bed, bed temperature, exhaust air at the temperature probe, and air immediately outside the equipment (e.g., room temperature), respectively.

To solve this equation, an extensive study is needed to characterize the additional variables introduced by this equation. Development of a general correlation using this equation is deemed impractical as

- the heat transfer area of equipment and ductwork ($A_{inl}$ and $A_{exh}$) is normally not available and not easily calculated
- the heat transfer coefficient of the room air ($U_{inl}$ and $U_{exh}$) depends on the ventilation of the room, which may not be characterized easily
the room air temperature ($T_r$) may not represent the air that surround the ductwork and equipment at the inlet (the inlet air temperature probe is often located in the mechanical area, where the temperature in this area may vary day to day)

Consequently, an empirical approach was taken in characterizing the heat loss.

**Validity of Constant Heat Loss Assumption**

An experiment was conducted in a lab-scale fully-perforated coating pan to determine the effective heat loss. Then using the same heat loss value, the exhaust temperatures at other operating conditions were predicted. The agreement between the measured and predicted exhaust temperatures at varying processing conditions was fairly reasonable as shown in Table 2. This suggested that the heat loss term does not vary significantly for a given coating unit if the process does not change drastically.

This test was repeated in a pilot-scale pan coater with a wider range of processing conditions. Again using the same heat loss value, predicted exhaust temperature and relative humidity results agreed well with measured results except at the highest exhaust temperature (57.7°C) tested (see Table 3). The actual heat loss at this temperature was 45% higher than the assumed value of 2.5 kW. It should be noted, however, that even with the 45% increase in the heat loss value, the exhaust temperature prediction was only off by 3°C.

Based on these results, it is concluded that under the test conditions examined in the lab and pilot-scale processes, the constant heat loss assumption provides reasonable prediction of process thermodynamics for given coating units. The practical implication of this finding is that the relationship between the independent and dependent variables for a coating process can now be estimated using Equations 1, 3 and 6. The utility of constant heat loss can be applied in product formulation, process development and scale up, and troubleshooting. Before presenting cases studies illustrating the utility of this finding, the role of process thermodynamics in drying kinetics is discussed to establish the relationship between the material, atomization, transport, and thermodynamic properties in drying kinetics.

**Drying Kinetics and Process Thermodynamics**

The drying of residual solvent in spray coating involves

1. evaporation of the solvent at the liquid-gas interface
2. diffusion of the solvent vapor through the coating film layer to the surface of the film, which is referred to as the internal mass transfer
3. diffusion of the vapor through the boundary layer around the coated surface into the bulk air, which is referred to as the external mass transfer

Both heat and mass transfer are involved in this process since heat must be added to offset the cooling due to evaporation. Only the mass transfer equations describing this process are considered below to illustrate the role of process thermodynamics in the drying kinetics.
Mass Transfer Equations

The equations describing the internal \((N_{a,int})\) and external \((N_{a,ext})\) mass transfer rate are given by (see, for example, Treybal\(^\text{5}\))

\[
N_{a,int} = k_{g,int} A_{int} (p_{a,f} - p_{a,s})
\]

\[
N_{a,ext} = k_{g,ext} A_{ext} (p_{a,s} - p_{a,b})
\]

where \(k_g\) is the mass transfer coefficient and \(A\) is the mass transfer surface area. \(p_{a,f}, p_{a,s},\) and \(p_{a,b}\) are the partial pressures of the solvent component \(a\) at the liquid-vapor interface, surface of the coat, and bulk air, respectively.

Noting that mass transfer surface area is approximately the same in these equations and the rates are equal at any given time, the Equations 8 and 9 can be combined to eliminate \(p_{a,s}\), resulting in

\[
N_a = \frac{A(p_{a,f} - p_{a,b})}{1 + \frac{1}{k_{g,ext}}} + \frac{1}{k_{g,int}}
\]

This equation shows the importance of the internal and external mass transfer in a resistance form. To illustrate the relative importance of the process thermodynamics variables in this equation, the coefficient for flow past a sphere\(^\text{6}\) with low solvent composition in air, is considered for the external mass transfer:

\[
k_{g,ext} = \frac{D_{ab,exh}}{R \cdot T_{exh} \cdot d} \left(2 + 0.6 \left(\frac{\rho_{exh} \cdot v_{exh} \cdot d}{\mu_{exh}}\right)^{1/2} \left(\frac{\mu_{exh}}{\rho_{exh} \cdot D_{ab,exh}}\right)^{1/3}\right)
\]

The coefficient for pore diffusion\(^\text{5}\) was considered for the internal mass transfer:

\[
k_{g,int} = \frac{D_{X,a,eff}}{R \cdot T_f \cdot z}
\]

Note that the external mass transfer coefficient is based on the environmental condition or process thermodynamics, but the internal mass transfer coefficient is based on the film condition. The mass transfer equation (Equation 10) can now be examined for two ideal scenarios.

Mass Transfer Rate at Low Spray Rate and Low Weight Gain

Most esthetic film-coating processes involve low weight gain and low spray rate. In these operations, the internal mass transfer coefficient is much larger than the external mass transfer coefficient (i.e., \(k_{g,ext} \ll k_{g,int}\) for a thin coating layer, \(z \rightarrow 0\)). At low spray
rate, the temperature at the surface of the target can be approximated by the exhaust air temperature and the mass transfer equation simplifies to

\[ N_a = k_{g,exh} A (p_{a,exh}^{sat} - p_{a,exh}) = k_{g,exh} A \cdot p_{a,exh}^{sat} (1 - RH_{a,exh}) \]  

(13)

\( RH_{a,exh}, T_{exh}, p_{a,exh}^{sat} \), and \( \rho_{exh} \) are thermodynamics properties, which are also process thermodynamics variables as defined earlier; \( D_{alb}, \rho_{exh}, \) and \( \mu_{exh} \) are transport properties; \( d \) and \( A \) are material properties; and \( A \) is also atomization property. The mass transfer surface area \( A \) is impacted by the initial distribution of the coating solution through the nozzle, and the distribution on the target surface through spreading of the coating solution as result of material properties. In this scenario, the process thermodynamics variables impact the drying rate as the primary driving force, and also impact the mass transfer coefficient.

**Mass Transfer at High Spray Rate and Large Weight Gain**

Many functional coatings, for example controlled-release coating and drug layering, involve large weight gain or high spray rate. In these operations, the evaporation rate of the solvent is limited by the transport of evaporated solvent through the film layer (i.e., \( k_{g,ex} >> k_{g,int} \)). Combining Equations 10 and 12 gives

\[ N_a = \frac{D_{K,a,eff} A (p_{a,f}^{sat} - p_{a,exh})}{R \cdot T_f \cdot z} = \frac{D_{K,a,eff} A \cdot p_{a,exh}^{sat} \left( \frac{p_{a,f}^{sat}}{p_{a,exh}^{sat}} \cdot RH_{a,f} - RH_{a,exh} \right)}{R \cdot T_f \cdot z} \]  

(14)

In this scenario, the process thermodynamics variables do not describe the entire drying rate because the film temperature could be considerably lower than the bulk air temperature. That is, \( D_{K,a,eff}, p_{a,f}^{sat} \), and \( T_f \) are transport and thermodynamics variables not directly related to the environmental condition or process thermodynamics. The material properties of the coating solution play a key role in developing the pore structure in the film and therefore could be considered the main factor impacting the solvent drying rate. In this case, the process thermodynamics variables are of lesser importance than for the mass transfer at low spray rate and low weight gain.

**Case Studies**

In the pharmaceutical industry, the product formulation is very much defined at the bio-batch stage (i.e., defined as batches made for clinical studies in at least one-tenth scale of manufacturing batches) and is difficult to change afterwards. Most subsequent product development activities focus on the process optimization, scale up, and tech transfer without changing the product formulation. These activities and troubleshooting activities after the transfer deal mainly with the process thermodynamics variables. That is, most of these activities deal with finding equivalent processing conditions in different scale equipment or analyzing deviations from the designed process during routine manufacturing. The process thermodynamics analysis can play a key role in these activities as illustrated in the case study examples below.
Case Study I: Determining Heat Loss and Exhaust Relative Humidity

Problem Description
For process optimization, scale up, troubleshooting, and design, the existing process must first be examined. In this case study, the process thermodynamics of a lab-scale coating unit is examined.

Process Analysis
The following process information is typically available as inputs from a lab unit:
- Process air flow rate – 1500 SLPM
- Process air temperature – 70°C
- Process air dew point temperature – air is drawn from the room, the room conditioning information is 50% RH at 20°C (i.e., \(T_d = 9.3°C\))
- Exhaust temperature – 45°C
- Spray rate – 5.8 g/min
- Atomizing air flow rate – 27.9 SLPM
- Fan air flow rate if pan coating is used – not used
- Solvent composition if solvent process is used – aqueous coating process used
- Solids content in the coating solution – 15%
- Pressure – open system therefore 14.7 psi used

Results
Based on the inputs above, the heat loss and relative humidity were determined by solving Equations 1, 3, and 6. The heat loss for the process was 0.54 kW and the exhaust relative humidity was 16.4%. This information can now be used to for process optimization in the same equipment and for scale up.

Case Study II: Process Bridging and Scale Up

Problem Description
The lab-scale process from Case Study I is to be scaled up to a commercial-scale process. Determine the thermodynamically equivalent condition at the commercial scale.

Problem Assessment
The thermodynamically equivalent condition here refers to the conditioning of the process including the temperature and humidity in the bed. This condition is assumed to be the same as that of the exhaust temperature and humidity. If the small- and large-scale equipment differs considerably in the amount of process air bypassing the bed, then this assumption will not be valid. The thermodynamically equivalent condition based on the lab-scale equipment is exhaust temperature of 45°C and RH of 16.4%.

Another consideration in the scale up is that the inlet air will no longer be drawn from the room, so the inlet air moisture content will be different. In large scale units, variations of humidity controls include
Complete humidity control—both humidification and dehumidification capabilities exist
Partial humidity control—desiccant wheel keeps humidity low
No humidity control

Assuming desiccant wheel is used in the large scale, the worst case scenario for humidity is in the summer time. Let’s say that on the most humid days, the desiccant wheel can only reduce the dew-point of inlet air to 4°C.

Procedure
To simulate the thermodynamically equivalent process at the commercial scale, the following variables are known:
- Exhaust relative humidity – 16.4% based on the lab-scale results
- Exhaust temperature – 45°C based on the lab-scale results
- Process air dew point temperature – 4°C based on the humidification capability described above
- Heat loss – 2.1 kW based on the commercial-scale equipment analysis
- Process air flow rate – in this example, the maximum controllable flow rate for the equipment of 3000 SCFM is chosen to maximize the equipment capacity
- Atomizing air flow rate – 15 SCFM
- Fan air flow rate if pan coating is used – 25 SCFM
- Inlet and exhaust pressures – open system, therefore 14.7 psi is used
- Solvent composition if solvent process is used – same aqueous coating process used
- Solids content in the coating solution – same at 15%

Results
Summary of the scale up data using thermodynamically equivalent condition is shown in Table 4. In order to maintain the same environmental condition as the lab-scale process, the spray rate and process air temperature need to be 593 g/min and 59°C, respectively.

Case Study III: Process Optimization

Problem Description
In order to make a better use of the equipment capacity, the process in Case Study II is to be further optimized. The batch size was already maximized for the equipment, so the only variable that could be altered to improve the capacity is the spray rate.

Use of Additional Development and Equipment Data
In order to increase the capacity of the commercial-scale process, additional data may be considered before embarking on a full-blown statistical experimentation. Additional lab-scale and pilot-scale data may be useful in determining experimental locations for the commercial-scale process. Another consideration is to assess the differences observed from previous transfers or scale ups—for example at the same thermodynamic condition, the tendency for over-wetting and agglomeration is greater in the smaller-scale process, therefore, the larger scale may tolerate higher relative humidity than the smaller scale.
process. Based on this information, an acceptable process range to examine in the commercial scale should be arrived at. The process thermodynamics relationship can be used to assess the capacity gain through increased spray rate by examining this acceptable process range.

Examples of useful lab- and pilot-scale data are as follows.
- Quality of coating is acceptable at exhaust temperatures up to 55°C
- Quality of coating is acceptable at exhaust RH up to 25%
- Coating solutions containing 18% solids can be made and sprayed without too much difficulty

Examples of useful equipment information are
- The blower can produce 3000 SCFM maximum process air flow rate
- The heater and ductwork can maintain 90°C maximum process air temperature at this process air flow rate

**Procedure**

The following inputs are to be used to calculate the optimal spray rate:
- Process air flow rate – 3000 SCFM
- Process air temperature – 90°C (using the exhaust temperature of 55°C results in a larger than 90°C process air temperature)
- Exhaust RH – 25%
- Solids content – 18%
- Process air dew point – 4°C (same as before)
- Heat loss – 2.1 kW (same as before)

**Results**

Solving Equations 1, 3, and 6 for spray rate gave 1900 g/min, which is about 320% increase in the capacity from the scaled up process in Case Study II, which was based only on the thermodynamically equivalent condition. This information can now be used to aid in the design of the commercial-scale experimentation.

The calculated exhaust temperature is 50.2°C, which is below the formulation-based limit of 55°C. In order to further increase the spray rate, the process air heater and the ductwork need to be modified to handle greater than 90°C.

**Case Study IV: Troubleshooting Manufacturing Deviation**

**Problem Description**

Product X is a combination-therapy product containing drug A in the core and drug B in the coating. During manufacturing of this product after a preventive maintenance procedure, one of the batches had a 10% lower drug B assay. Find the root cause of this 10% decrease in drug assay for this batch. In this process, the drug is layered onto the tablets. The only deviation observed from the process data was 2°C increase in the exhaust temperature.
**Suggested Solution**

This deviation may be the result of a deviation in an operational procedure or a malfunction of process instrumentation. Both need to be considered in screening out potential variables that can increase the exhaust temperature and decrease drug applied on the tablets. The process thermodynamics relationship in Equations 1, 3, and 6 can then be used to quantify the deviation such that the probabilities of these occurrences can be assessed.

**Screening of Process Variables**

Potential variables are listed in Table 5 and analyzed for their impact on both the exhaust temperature and coating assay. Based on the inspection of potential variables, the only variables that can affect both temperature and assay are solids content in coating solution and spray rate.

**Analysis of Normal Manufacturing Process**

The first step is to characterize the normal manufacturing process. That is, determine the heat loss for the normal operation based on the process data using the process thermodynamics relationship in Equation 1, 3 and 6. The inputs needed are

- Process air flow rate – 2000 SCFM
- Process air temperature – 71°C
- Process air dew point temperature – 10°C
- Exhaust temperature – 49°C
- Spray rate – 1050 g/min
- Atomizing air flow rate – 10 SCFM
- Fan air flow rate if pan coating is used – 15 SCFM
- Solvent composition – 56.5% methanol and 44% water
- Solids content – 30%
- Inlet and exhaust pressures – 14.7 psi

The heat loss calculated from the process thermodynamics analysis is 1.91 kW.

**Simulation of Solids Content Deviation**

The second step is to simulate the deviation, i.e., determine the magnitude of change needed to effect the 2°C change in the exhaust air temperature. For the consideration of the solids content in the coating solution, the following inputs are chosen

- Process air flow rate – same value
- Process air temperature – same value
- Process air dew point temperature – same value
- Exhaust temperature → increase the normal value by 2°C to 51°C
- Heat Loss → 1.91 kW calculated from the analysis of the normal operation

Using trial and error approach in solving Equations 1, 3, and 6, the coating-solution solids content was changed until the same spray rate (1050 g/min) was achieved. The simulation results showed that the solids content would have to be changed from 30% to
37% in order to cause the 2°C rise in the exhaust temperature. If this were true, the resulting assay should have been increase by 23% (= (37-30)/30), but the assay decreased by 10% in actuality.

**Simulation of Spray Rate Deviation**

The following inputs were used to simulate the spray rate deviation:
- Process air flow rate – same value
- Process air temperature – same value
- Process air dew point temperature – same value
- Exhaust temperature → increase the normal value by 2°C
- Heat Loss → 1.91 kW calculated from the analysis of the normal operation

The simulation of this condition gave the spray rate of 944 g/min, which is 10% lower spray rate from the original 1050 g/min. This 10% reduction in spray corresponds exactly to the 10% decrease in the drug assay.

**Analysis of Results**

The process thermodynamics calculations showed that 2°C change can be the result of inlet air flow rate, inlet air temperature, solids content, and spray rate. However, inlet air flow rate and temperature do not impact the amount of coating on the tablet, so these are not likely causes for the 10% change in drug assay. Solids content affects drug assay, but the thermodynamics analysis shows that 2°C increase in exhaust temperature should have increased the drug assay, not decrease it. On the other hand, the change in spray rate to effect a 2°C rise in exhaust temperature was calculated to be 10% decrease in spray rate, which corresponds exactly to the 10% decrease in drug assay. Based on this analysis, the most likely cause of the 10% decrease in the drug assay and 2°C increase in exhaust temperature is the spray rate.

**Case Study V: Solvent Formulation Optimization**

**Problem Description**

Methanol is used to dissolve a control-release coating compound. Research data shows complete solubility of this compound can be achieved at greater than 50% methanol. Determine the solvent mixture of water and methanol that maximizes the capacity (i.e., spray rate in this case) under the following constraints:
- Exhaust temperature must be held at 38°C to minimize defects
- Exhaust relative humidity must be kept at 17% to minimize sparks as result of static and to minimize agglomeration
- The blower is capable of providing up 3000 SCFM
- Maximum expected dew-point of the process air is 5°C using the desiccant dryer

The two scenarios to examine are with and without bypass
- Without the bypass air, LEL must be kept below 20% for safety
- With the bypass air, process LEL can go up to 40%, but the diluted LEL must be kept below 20%
Without Bypass

For this problem, the methanol content must be changed that maximizes the spray rate. Inputs for this calculation are

- Exhaust temperature – 38°C
- Exhaust RH – 17%
- Inlet air dew-point temperature of 5°C
- Process air flow rate – 3000 SCFM
- Heat loss must be specified – if data not available, analyze an existing process to estimate the heat loss

To solve this multi-component solvent system, Equation 6 must be solved for both methanol and water components, and an equation describing LEL as function of temperature is needed. The details of these equations are not shown here. Instead, a commercially available process thermodynamics tool was used to solve this problem. A snapshot of the simulator window is shown in Figure 2 for this problem. The maximum spray rate of 1740 g/min could be obtained by changing the compositions of water and methanol until 20% LEL was achieved with zero bypass air flow.

With Bypass

The above procedure was repeated with the bypass air to achieve 40% LEL at the process exhaust. Then, the bypass air was increased until the diluted LEL was 20%. The resulting maximum spray rate was 3290 g/min.

Analysis of Results

Without the bypass air, the maximum spray rate of 1740 g/min could be achieved with 87% methanol composition in the coating solution. The spray rate went up to 3290 g/min (a 89% increase) with the bypass air using 92% methanol. Note that doubling the LEL allowance did not result in doubling of the spray rate.

Case Study VI: Process Design – Alarm and Shutdown Limits

Problem Description

Determining the process robustness range and building controls around this range is considered part of the process design. For the optimized process results in Case Study III, the proposed controls on the air flow rate and dew point are ±200 SCFM and ±2°C, respectively. The development data showed that significant over-wetting is not observed as long as the exhaust relative humidity is kept below 28%. Are the controls around the air flow rate and dew point acceptable for this process?

Problem Assessment

The optimized process from Case Study III is as follows:

- Process air flow rate of 3000 SCFM
- Process air temperature of 90°C
- Process air dew point of 4°C
• Exhaust relative humidity of 25%
• Exhaust temperature of 50°C
• Spray rate of 1880 g/min

**Analysis of Results**

The results shown in Table 6 at the suggested limits on air flow and dew point indicate that the control of air flow rate is more important than the dew point for this process, and that air flow rate must have a tighter tolerance in order to meet the 28% RH cap. The tighter tolerance of ±100 SCFM and the same tolerance of ±2°C dew point resulted in the worst possible relative humidity of 28.4%, which may be acceptable based on the development data. Alarm and shutdown limits may be designed around these results.

This same procedure can be applied to all process control variables in determining the alarm and shutdown limits.

**Case Study VII: Statistical Experimental Design**

**Problem Description**

Independent variables are typically used in the design of experiment. However, in some experiments it may be desirable to use dependent variables as the control variables for the experiment if

- dependent variables are linked directly to quality attributes—for example, relative humidity is sometimes linked with the amount of attrition observed in the fluid bed coating process
- relationship between the dependent variables and independent variables are known

In this case study, the amount of film defect is being assessed at various coating conditions. It is believed that the dependent variables relative humidity and exhaust temperature are strongly linked with the amount of defects. Consequently, the controls of the statistical design are exhaust RH and exhaust temperature. The task at hand is to determine the setting for the process control variables if a two-level, three-variable full-factorial experiment (i.e., $2^3$) is being designed around the dependent variables exhaust RH and temperature.

**Problem Assessment**

The locations of the experiment are chosen based on preliminary studies, but it is not clear if these conditions are feasible from equipment capability standpoint:

- 40 and 48°C for exhaust temperature
- 15 and 25% for exhaust relative humidity
- 100 and 300 g/min for spray rate

The inlet air dew point is 6°C, the heat loss for the equipment is approximately 2.5 kW, atomizing air is 30 SCFM, and the aqueous coating solution contains 10% solids.
Simulation of Experimental Conditions
The process thermodynamics equations are used to determine the values of process air flow rate and temperature to arrive at the above experimental locations. The simulation inputs for the ‘---’ location is shown below as an example:

- Exhaust temperature of 40°C
- Exhaust relative humidity of 15%
- Spray rate of 100 g/min
- Heat loss of 2.5 kW
- Process air dew point temperature of 6°C

Analysis of Results
The simulations of all experimental locations are shown in Table 7. Runs # 2 and 7 are outside the equipment capability, therefore, these runs may be omitted. To further reduce the number of experiments, a fractional design may be used.

Note that a constant heat loss value was used for these calculations. Because the processing conditions vary widely, the heat loss value likely will not be constant. A preliminary experiment is recommended to determine the heat loss values at these conditions and refine the processing conditions to match the exact experimental locations.

Conclusions
The relationship between the process thermodynamics variables and process control variables were derived from steady-state material and energy balance equations. However, the analysis of the variables in the equations pointed to the fact that additional information was needed to solve the equations. Experimental investigation of heat loss revealed that the heat loss remained relatively constant if the process did not change drastically. Using this finding, the utility of the process thermodynamics was illustrated through case studies on process analysis, optimization, scale up, troubleshooting, formulation, controls design, and experimental design. Although the experimental results and case studies in this article used pan-coating systems, the process thermodynamics analysis can be applied to any spray coating and spray drying processes.

The role of process thermodynamics was also investigated using mass transfer rate equations. The analysis showed that process thermodynamics is very important for the control of the drying rate at low spray rate and low weight gain. However, at high spray rate and large weight gain, the coating solution formulation can control the drying rate.

Acknowledgements
Vector Corporation of Marion, IA is acknowledged for their contribution in providing the equipment and manpower generate the heat loss data used in the paper.
**Symbols**

$A$  Mass transfer surface area
$C_p$  Heat capacity
$d$  Target diameter
$D_{ab}$  Diffusion coefficient for constituent $a$ in medium $b$
$D_K$  Knudsen coefficient
$k_g$  Mass transfer coefficient
$N$  Mass transfer rate
$P$  System pressure
$p$  Partial vapor pressure
$p_{sat}$  Saturation vapor pressure
$Q$  Volumetric flow rate
$R$  Universal gas constant
$RH$  Relative humidity
$T$  Temperature
$T_d$  Dew-point temperature
$U$  Overall heat transfer coefficient
$v$  Velocity
$W_{sp}$  Spray rate
$x$  Composition in liquid phase
$y$  Composition in gas phase
$z$  Coating thickness
Greek Symbols

$\lambda$  Latent heat of vaporization
$\mu$    Viscosity
$\rho$   Density
$\Delta H_{\text{loss}}$  Heat loss
$\Delta T_{LM}$  Log-mean temperature difference

Subscripts

$a$      Pertaining to component $a$
$at$     Pertaining to atomizing air
$b$      Pertaining to bulk air
$exh$    Pertaining to exhaust condition
$ext$    Pertaining to external mass transfer
$f$      Pertaining to film
$fan$    Pertaining to fan air
$inl$    Pertaining to inlet air (process air) at the temperature probe
$inl,2$  Pertaining to inlet air condition just before the temperature probe
$int$    Pertaining to internal mass transfer
$r$      Pertaining to room or air surrounding the equipment
$s$      Pertaining to solids in the coating solution
$sol$    Pertaining to solvent
$\tau_d$ At dew-point temperature


References