

This article introduces a state-of-the-art method to track conditions for wet processes that provides continuous operating guidance through a combination of measured and calculated values.

Introduction to Real Time Process Determination

by Kim Walter

Many processes in the pharmaceutical industry require mixing of active pharmaceutical ingredients with inactive powders to transform the mixture into useful solid dosage material. Frequently, the process incorporates the use of water or organic solvents, the so-called wet processes such as drying of granules from a mechanical mixer, spray granulation of the product in a fluid bed, pellet coating for taste masking, pellet coating to modify drug release characteristics, and powder laying of the active drug on an inactive powder.

To produce to specification, wet processes generally require control of the humidity in the process chamber, although in some cases, control of temperature or partial pressure is critical. For organic solvents, instruments cannot measure the relative humidity inside the process vessel. Common practice is to use a trial and error procedure, changing process conditions until all parameters are within tolerances. This procedure is both difficult and wasteful, depending mostly on the insight and decisions of process developers and experienced operators.

Real time process determination™ is a state-of-the-art method to track conditions for wet processes that provides continuous operating guidance through a combination of measured and calculated values. It may be used to control a continuous or a batch process through all of its steps and transitions, regardless of variations in ambient or process conditions. It gives the skilled process developer easy-to-interpret information in the form of a chart that guides the decision process.

Process Variables

Pharmaceutical production demands consistent results, which are very difficult to achieve with batch processes since each batch is slightly different. To apply real time process determi-

nation, the target conditions must be defined - endpoint humidity for drying, solvent encapsulation and applied membrane characteristics for pellet coating, residual moisture in tablet pressing, etc. Theoretically, if the process variables are consistently on target, the specifications of each batch will be identical.

However, running a process in precisely the same way time after time is impossible, and even very small deviations can have a significant influence on the end result. Different response times for the process variables also may be a factor when adjustments are made during production - a change in the spray rate affects the process nearly instantly, while a change in the inlet temperature has a much longer response time.

A preferred thermodynamic condition exists in the process chamber in order to achieve consistent results. Using coating and spray granulation as an example, variables are feed rate, inlet temperature, and spray rate of solvent. The thermodynamic condition can be given as a particular combination of relative humidity and temperature - the target condition. In this case, only two process variables must be controlled during the process instead of all three. In some processes, one of these conditions, relative humidity or temperature, may be more critical than the other. Therefore, the critical variable becomes the primary target condition and the not-so-critical variable becomes the secondary target condition, enabling the critical target condition to be reached faster. If there is a deviation in the target temperature in the process chamber - the process variable with the longest response time - the spray rate can be adjusted, which has the shortest response time, which will change the temperature nearly instantly. The process gas flow rate can be changed, which has a median response time, if we want the target temperature to react over a short time interval.

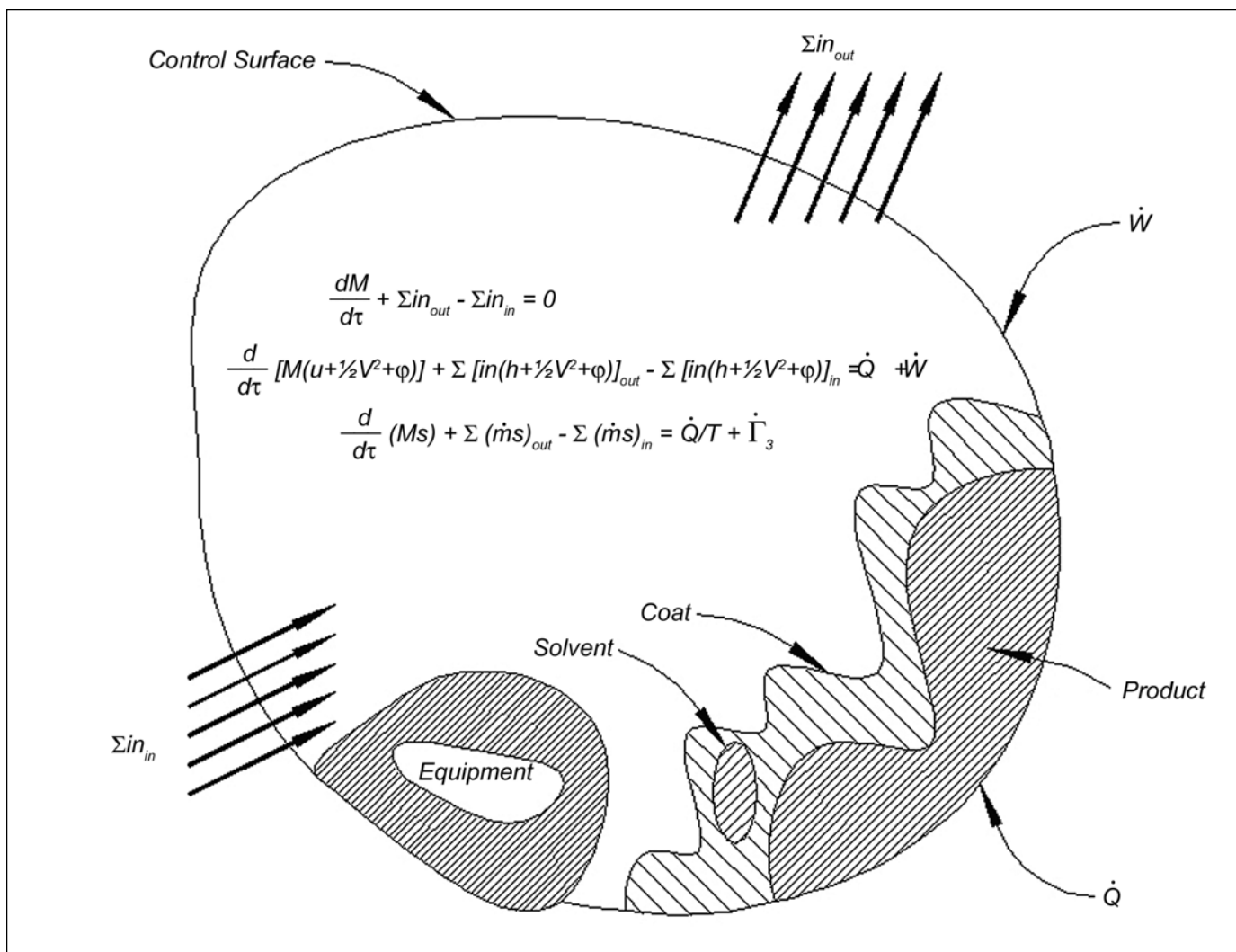


Figure 1. Thermodynamic model for real time process determination.

Usually, only the process variables are controlled, without knowing the thermodynamic target. However, if thermodynamic laws are applied to the equipment, the thermodynamic condition in the process chamber can be determined, and by experimenting with different conditions, the critical thermodynamic condition can be determined. With the critical thermodynamic condition specified, the scale-up and transfer from equipment to equipment become easier. Choosing the thermodynamic condition for controlling the process, instead of using only the single loop recipe control, will ensure more reproducibility of both batch and continuous processes. This is the basic objective of real time process determination.

The Thermodynamic Approach

The thermodynamic approach is built on two fundamental laws, conservation of mass and conservation of enthalpy. The law of conservation of mass says that the change of mass inside a closed system in time is equal to the flux of mass entering the closed system minus the flux of mass exiting. The law of conservation of enthalpy says that the change of enthalpy inside a closed system in time is equal to the flux of enthalpy entering the closed system minus the flux of enthalpy exiting.

Figure 1 shows the heat and mass balance of the thermodynamic system used on the process equipment. The control surface represents the equipment walls. Through the inlet enters some mass flow of process gas, atomizing gas, spray liquid (which may consist of several solvents), solvent vapor in the process gas, and solids suspended or dissolved in the spray liquid. Through the outlet flows the process and atomizing gases, which will contain some solvent vapor. The difference in the mass flow of solvents from the inlet to the outlet is what is added or removed from the product over time. The amount of solvent inside the equipment, which is not evaporated, is depicted as an area on the drawing.

The enthalpy balance consists of the enthalpy flowing out minus the enthalpy flowing into the equipment. The divergence in the enthalpy flow is the change in the enthalpy level inside the equipment and the heat flow “Q” through the equipment wall. The term “W” depicted on the drawing is the work done on the system.

The last thermodynamic term we need to understand is adiabatic. A process is adiabatic when the heat change inside the closed system happens without exchange of heat with the surroundings. When the process is adiabatic, the enthalpy is constant. So if the heat loss from the equipment is identified,

the exchange of the enthalpy inside the equipment walls can be calculated.

Equations to Determine Physical Values

Five physical values are important to the process:

1. The temperature, which can be measured.
2. The pressures, including ambient pressure, total pressure, and partial pressures of each component. The total pressure is the sum of the partial pressures of each individual gas and the partial vapor pressure of the solvents. The partial solvent pressure (vapor pressure) is the amount of the particular solvent present in the gas. The saturated vapor pressure is the maximum pressure the particular solvent can have at a given temperature.
3. The concentration of solvent, also called the specific humidity – the mass of the particular solvent dissolved per mass unit of gas.
4. The dewpoint temperature, at which, for a given solvent concentration (specific humidity) and total pressure, the gas/solvent mixture is saturated.
5. Specific heat capacity - the amount of heat necessary to increase a mass unit of the product, the particular solvent as vapor or liquid, and the gas, one degree.

To connect the thermodynamic laws, the equations of the five physical values must be used. The relative humidity is calculated as the ratio between the actual specific humidity and the saturated specific humidity in percent for a given gas temperature. The relative humidity also is the ratio between the actual vapor pressure and the saturated vapor pressure in percent for a given gas temperature. The relative humidity for the solvent $\{i\}$ is expressed by the equation:

$$j_{solvent\{i\}} = \frac{p(\text{partial} - \text{pressure})_{solvent\{i\}}}{p(\text{saturated} - \text{pressure})_{solvent\{i\}}}$$

For water, there are instruments that measure the electric resistance of the air, which depends on the concentration of water vapor. This measurement, in combination with the air temperature, enables the calculation of the relative humidity for water vapor. Since instruments cannot measure the relative humidity of an organic solvent; it must be calculated.

The relation between the relative and the specific humidity can be calculated:

$$x_{solvent} = \frac{M_{solvent} j_{solvent} p(\text{saturated})_{solvent}}{M_{gas} [p_{total} - j_{solvent} p(\text{saturated})_{solvent}]}$$

where $M_{solvent}$ is the molecular weight for the particular solvent and M_{gas} is the molecular weight of the process gas.

The enthalpy, the heat content of a mass unit of gas, is calculated as the specific heat capacity of the gas plus the sum

| | |
|--------------------------------------|--|
| M | = sum of mass (product, equipment, coat, solvent, and gas) inside the control volume [kg] |
| t | = time [sec] |
| \dot{m}_{in} | = mass flow into the control volume [kg/sec] |
| \dot{m}_{out} | = mass flow out of the control volume [kg/sec] |
| u | = inner energy [Joule/kg] |
| h | = enthalpy [Joule/kg] |
| V | = velocity [m/sec] |
| s | = entropy [Joule/kg] |
| \dot{Q} | = heat [Joule/sec] |
| \dot{W} | = work [Joule/sec] |
| \dot{C}_s | = entropy production [Joule/Kelvin*sec] |
| $j_{solvent\{i\}}$ | = relative humidity for the solvent $\{i\}$ [%{saturated}] |
| $p(\text{partial})_{solvent\{i\}}$ | = partial pressure of solvent $\{i\}$ [Pascal] |
| $p(\text{saturated})_{solvent\{i\}}$ | = saturated pressure of solvent $\{i\}$ [Pascal] |
| P_{total} | = sum of the gases and solvents partial pressure [Pascal] |
| $x_{solvent}$ | = general mass ratio between particular solvent and the gas [kg/kg] |
| $M_{solvent}$ | = molecular weight of the solvent [kg/kmol] |
| M_{gas} | = molecular weight of the process gas [kg/kmol] |
| h | = enthalpy, heat content per mass unit of gas [Joule/kg] |
| T | = temperature [Celsius] or [Kelvin]. If Kelvin is used in the enthalpy equation, all values have to be expressed in Kelvin |
| T_{ref} | = chosen reference temperature, normally 0°C |
| $C_{p_{gas}}$ | = specific heat capacity of the process gas [joule/kg*8C] |
| $C_{p_{sol}}$ | = specific heat capacity of the solvent vapor [joule/kg*8C] |
| $\dot{s}\{i\}_{solvent}$ | = mass flux of the solvent $\{i\}$ entering the control volume as liquid into the control volume [kg{solvent}/sec] |
| $x_{product}$ | = specific humidity on product surface in a coating process |
| $x_{ambient}$ | = ambient specific humidity [kg{solvent}/kg{gas}] |
| $\dot{m}_{process-gas}$ | = flux of process gas mass flow rate entering or leaving the control volume [kg{gas}/sec] |
| $r_{solvent}$ | = heat of evaporation for the solvent at the reference temperature [Joule/kg{solvent}] |

Table A. Nomenclature.

of the specific humidities of the solvents times their specific heat capacities, taking the entire sum times the temperature plus the specific humidity of the solvents times their heats of evaporation.

$$h = \int_{T_{ref}}^T [c_{p_{gas}}(T) + \sum_{i=1}^{i=n} x\{i\}_{solvent} c_{p_{sol}}(T)] dT + \sum_{i=1}^{i=n} x\{i\}_{solvent} r_{solvent}(T_{ref})$$

The term $x\{i\}$ is the mass ratio of the particular solvent $\{i\}$ dissolved as vapor in the process gas. The total pressure of the gas plus the sum of the partial pressures of the solvents, which is the ambient pressure, is constant. When the solvents are dissolved in the gas, the gas volume will expand, lowering the density of the gas. If the solvent is water, the change in density of the gas is negligible since the amount of water vapor that can be dissolved before the mixture becomes

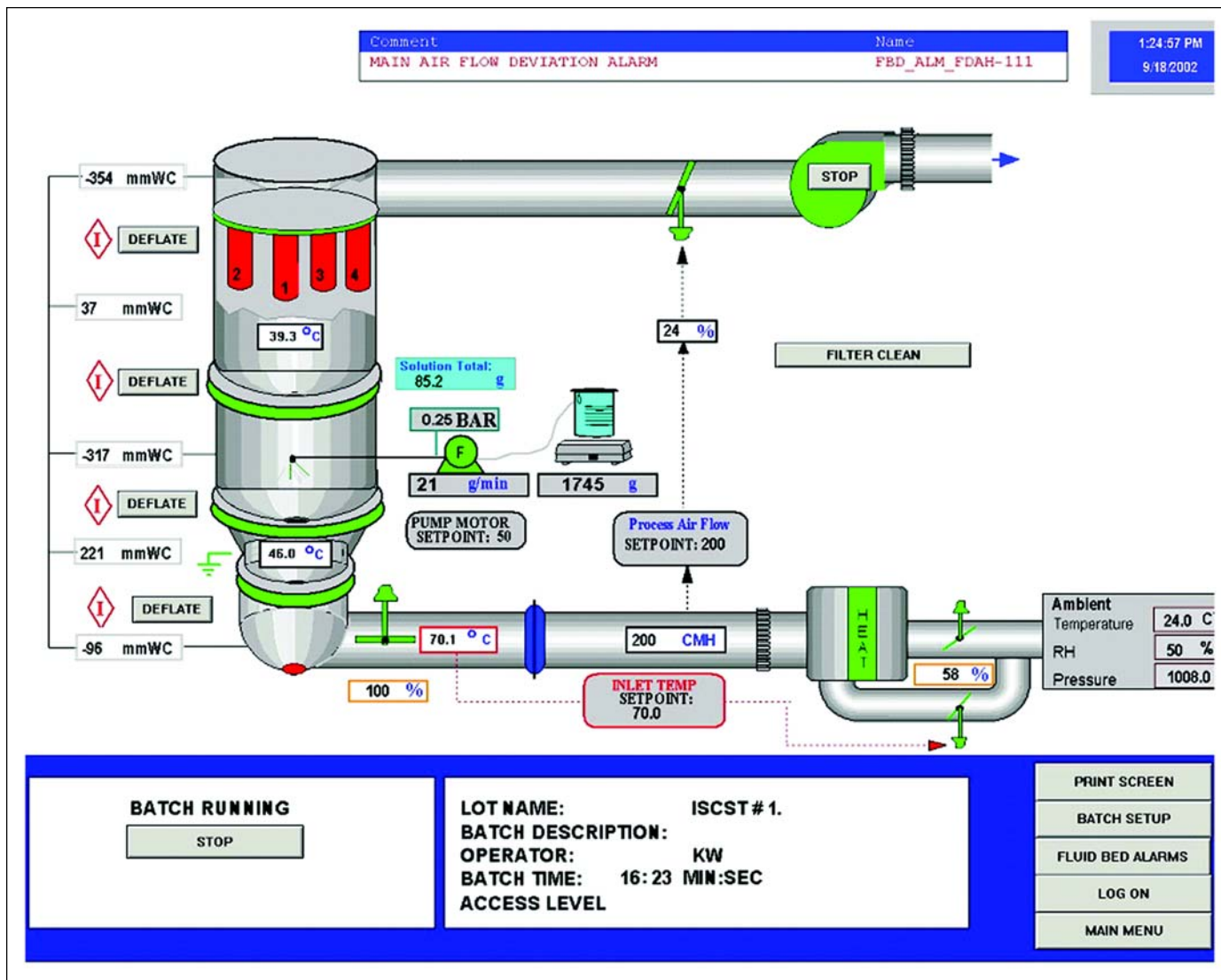


Figure 2. Automation control screen for typical multi-purpose process equipment.

saturated is small. When a mixture of solvents is present during the process and some of the solvents are volatile, the change in gas density has to be taken into consideration. The enthalpy gives the value of the gas and the vapor heat content, calculated from a chosen reference temperature, T_{ref} , which normally is the triple point of water 0°C. The term $r_{solvent}$ in the equation for the enthalpy is the evaporation heat for the particular solvent i at the reference temperature.

All the values in these three equations are physical material properties and are a function of the temperature. The values have been measured by many people over the last hundred years, published in tables, and organized as a physical-chemical database. Over time, many have converted the physical-chemical data table into mathematic formulae with the use of different approximations. The equations that approximate the physical-chemical data seem at first glance complicated. However, with current computer capacity, the task is possible.

With a further analysis of the three equations, it can be concluded that if two of the four values are known, the two

other values can be calculated. However, if all four values are known and two values are enough to determine the thermodynamic condition, it produces six different ways to solve the equations. This sounds strange, because if the values are known, why calculate them? The answer is: there is more information from the normal control system than is needed to determine the thermodynamic condition. This allows us to determine the unknown values in the thermodynamic models, such as heat loss, heat exchange, measuring errors, and so on.

Determining the Thermodynamic Condition

For a given process, the inlet, product, and outlet temperatures from the control system can be obtained. The flow rate of process gas is known, as is the concentration of solvent in the inlet gas (known from the inlet gas dewpoint temperature). Again, using spray granulation or coating as an example, the amount of solvent added to the process is known. The ambient pressure is either measured or can be assumed to be normal atmospheric pressure, 1013 hPa.

The first calculated value is the enthalpy of the inlet gas.

The equipment is started empty, with a given inlet temperature and process gas flow rate, and observed. In an adiabatic process, the product and outlet temperatures should rise to the inlet temperature as the equipment warms up. This is not the case; the system or the equipment is non-adiabatic for two reasons: the heat loss through the equipment wall and the heat transfer from the process gas to the equipment, both of which change the temperatures. The product and outlet temperatures will start out lower than the inlet temperature and gradually increase as the system reaches a steady state. After some time has elapsed, the product and outlet temperatures will approach fixed values. At this point, the outlet temperature will normally be lower than the product temperature. Two important inherent features of the particular equipment being tested has been observed: the time response and the effect of the heat loss through the equipment wall, both unique for this equipment. By repeating this procedure with different process gas flow rates and inlet temperatures, the heat loss of the particular installation can be determined. If the same procedure is executed with different products and product loads, information is determined about the total system's heat loss and time response. The heat loss can then be calculated, so with both the equipment running empty and with product being processed, the real inlet temperature can be determined.

The next investigation should be the accuracy of the process gas measurement. Measuring the flow rate is difficult and frequently inaccurate. The best example to use in an investigation of the gas flow measurement is coating. In the coating process, processing time is normally long enough for the equipment to reach steady state. With the knowledge about the heat loss, the real inlet enthalpy is known. In coating, a small amount of residual solvent is encapsulated in the coat; therefore, the process is close to adiabatic. Assuming an adiabatic process, the enthalpy of the inlet and the enthalpy on the surface of the product must be the same. Using the equation for the inlet condition with the modified inlet temperature, the specific humidity of the inlet gas, and the rate of process gas, the inlet enthalpy is known. Measuring the product temperature and the spray rate, the relative and specific humidity on the product surface can be determined. The specific humidity on the product surface is the ambient specific humidity and the added solvents from the spray divided by the process gas mass flow rate:

$$x_{product} = x_{ambient} + \frac{\sum_{i=1}^{i=n} \dot{s}(i)_{solvent}}{\dot{m}_{process-gas}}$$

Performing this procedure with different process gas flow rates and spray rates will reveal the deviation between the measured process flow and the actual flow rate. With the two corrections, the heat loss and the deviation between the measured and calculated process gas rate, the relative humidity in the process chamber can now be calculated at any given time.

The customary control procedure in coating is to adjust the

spray rate according to the product temperature. The product temperature is governed by the spray rate and the time response due to the thermal heat exchange between the process gas and the equipment and product mass. The product temperature is measurable and real and the calculation of the specific humidity, based on the equation, will give the actual relative humidity on the product surface. Combining the "two" relative humidities, one based on constant enthalpy and one on spray rate/process gas mass flow, will provide the adiabatic ratio, or how far the process is from adiabatic. When the steady state is reached, the adiabatic ratio equals one.

Using the Thermodynamic Calculation to Guide the Process

The thermodynamic calculations utilize the information from the control system. Determining the numerical values from the equations is complex and time consuming, so the obvious choice is to use a computer program. When this is written and data are input from the control system, the logical step is to bring the computer program and the control system together as one unit and calculate the thermodynamic conditions in real time. With the real time calculation, the program also can calculate how much each of the process values has to be changed to bring the process to the target conditions. The program calculates all possible changes and the consequence of each single change. There are a total of 12 changes and eight consequences to choose among, depending on which final thermodynamic condition the process demands. The final challenge is to display the possible choices in a comprehensive way.

Instruments make available information visible, putting the operator in the best possible position for making an optimal decision. Figure 2 shows a control screen for a typical multi-purpose process scheme. This familiar configuration uses a combination of flow diagram and equipment schematic to display measured physical conditions such as temperature, pressure, and flow rates, as well as setpoints for process variables.

To display calculated conditions in addition to measured, a real time process determination screen may be added to the control panel - *Figure 3*. In the case of bottom spray coating, where the relative humidity in the process chamber has the highest priority, the value can be calculated and displayed. Because the change in the relative humidity is a result of changes in three other process variables (inlet temperature, solution spray rate, and process gas flow rate) the deviation meter shows the results from the calculation and displays the proper action to take. The operator can, in a single glance at the meter, take in all three values which can be changed (the gold-colored lines), and how much each of the values has to be changed to reach the desired condition.

Experience dictates that the combination of analog and digital displays is the best way to notify the operator about current and desired conditions. On the deviation meter, the three set points are shown both graphically and digitally. Because bottom spray coating is a dynamic process with a long response time for one of the observed values (the process

chamber temperature), the operator also has to be informed about the time development of the process. This also is a combination of analog and digital information. The digital information is given by the adiabatic ratio. This is calculated as a ratio between the evaporation rate (based on a combination of the spray and process gas rates) and the measured temperature difference between the inlet and process chamber temperature. This number provides information on the current adiabatic ratio, but to make the dynamics of the adiabatic ratio visible, a new method had to be developed.

The Adiabatic Ratio Instrument

The layout of the adiabatic ratio instrument has been influ-

enced by the opinion that few persons can comprehend values that are not given in a linear form. Some observers even go as far as to say that no person can comprehend magnitude. We seem all better equipped to comprehend linear changes than changes in magnitude.

Relative humidity is based on the saturated vapor pressure as a function of temperature. The saturated vapor pressure increases with around the sixth power of temperature; therefore, a small increase in temperature creates a large change in relative humidity. The aim has been to find a way to display the relative humidity in linear form. The solution is a dynamic psychrometric chart or the dynamic specific humidity diagram - *Figure 3*.

The Thermodynamic Equations

Figure 1 represents the basic thermodynamic system for a control volume. The three equations are conservation of mass, conservation of enthalpy, and increase in entropy.

The control surface is an imaginary boundary, chosen so that the fluxes crossing the boundary are known values or can be determined. The fluxes are the mass flow, \dot{m} , the sum of all gases, vapors, liquids, and solids flowing in and out of the control volume. The term \dot{W} is the work applied to the control volume. In this specific case of real time process determination, the work applied is the movement of the process gas and the product inside the control volume, in short: the pressure loss experienced by the fan. The term \dot{Q} is the heat passing over the boundary of the control volume. In the case of real time process determination, the heat is the heat loss through the equipment wall.

The first equation, conservation of mass, expresses the change of mass in time inside the control volume plus the flux of mass out minus the flux of mass in. This is equal to zero. The mass inside the control volume is represented by M , where M is the sum of the equipment wall, the product, the solid delivered to the product as coat or layering material, and the solvent retained in the product, coat, or applied material (all the solvent that has not evaporated).

The second equation, conservation of enthalpy or the first law of thermodynamics, expresses that the change of enthalpy in time inside the control volume plus the flux of enthalpy out minus the flux of enthalpy in, is equal to the delivered heat and work flux to the control volume. The term $(u + \frac{1}{2} V^2 + n)$ is the energy. The u is the internal energy of all the material inside the control volume except the kinetic energy and potential energy. The numerical value of u is assumed to be zero at the temperature scale zero point. The term $\frac{1}{2} V^2$ is the kinetic energy of the material inside the control volume, where V is the velocity. The n is the chemical potential of the material inside the control volume. The term $(u + \frac{1}{2} V^2 + n)$ is expressed in joules. In the term representing the mass flow in and out of the control volume, the internal energy u is replaced by

$h, (h + \frac{1}{2} V^2 + n)$, where h is the heat content of the material entering and leaving the control volume.

The third equation, increase in entropy or the second law of thermodynamics, expresses that the change of entropy in time inside the control volume plus the flux of entropy out minus the flux of entropy in, is larger than the heat conveyed over the boundary of the control volume divided by the control volume's absolute temperature.

$$\frac{d}{dt} (Ms) + \sum (\dot{m}s)_{out} - \sum (\dot{m}s)_{in} \geq \frac{\dot{Q}}{T}$$

In order to balance the equation, the production of entropy inside the control volume must be added. The term \dot{G}_s expresses this production of entropy inside the control volume in joule/KelvinBsec. The M, \dot{m} and \dot{Q} are the same as in the first and second equations. The s is the entropy from Gibbs equation. For the determination of the entropy difference between the entering and exiting flow, we look at an example. For a simple compressible substance $s = s(u, v)$, the entropy s is a function of the inner energy u and the volume per unit of mass v . Differentiate the function and we obtain:

$$ds = \frac{\partial s}{\partial u} du + \frac{\partial s}{\partial v} dv$$

Using the thermodynamic definitions of temperature and pressure, we find:

$$ds = \frac{1}{T} du + \frac{P}{T} dv$$

Therefore the difference between the entropy s_{out} and s_{in} is:

$$s_{out} - s_{in} = \int_{u_{in}}^{u_{out}} \frac{du}{T} + \int_{v_{in}}^{v_{out}} \frac{P}{T} dv$$

The entropy s is expressed as joule/Kelvin.

Along an adiabatic line, the temperature and the specific humidity are nearly linear. So if the values of the ambient condition, inlet, process chamber, and outlet conditions are represented as the specific humidity and used as ordinate, the relations of these conditions are linear. Now the specific humidity of each relative humidity value along the inlet enthalpy line can be calculated. The 100 percent relative humidity, or saturated condition, gives the maximum ordinate value. The abscissa value is time. From testing it is known that the time response is from 20 to 45 minutes so this is the length of the chart. The background of the chart is the relative humidity expressed as specific humidity.

The process conditions - ambient condition, inlet, process chamber, and outlet condition - are shown in relation to the relative humidity. As the inlet temperature increases, the saturated value of the specific humidity increases also, so the dynamic psychrometric chart grows. When the inlet temperature decreases, the saturated value of the specific humidity also will decrease, so the chart shrinks. When the process is adiabatic, the specific humidity based on the spray/process gas flow rate and the specific humidity of the process chamber

temperature will be equal, so the two curves will overlap. When the process is non-adiabatic, the specific humidity of the combined spray/process gas flow rate and the specific humidity of process chamber temperature will be two different values, so the two curves will be separated.

With one glance at the dynamic psychrometric chart, the operator can evaluate if the process is adiabatic or non-adiabatic, and how far from adiabatic the process is in the current situation. Thus, the operator sees information in a linear form indicating how much the spray rate can be increased by evaluating the distance from the ambient condition to the curve showing the specific humidity of the spray/process gas flow rate with the specific humidity line representing the target relative humidity. People who have worked with the system find the dynamic psychrometric chart easy to understand and say that it makes the decision process fast and easy.

An Example of Real Time Process Determination

Using the example of a bottom spray coating process, the thermodynamics process screen contains both actual and

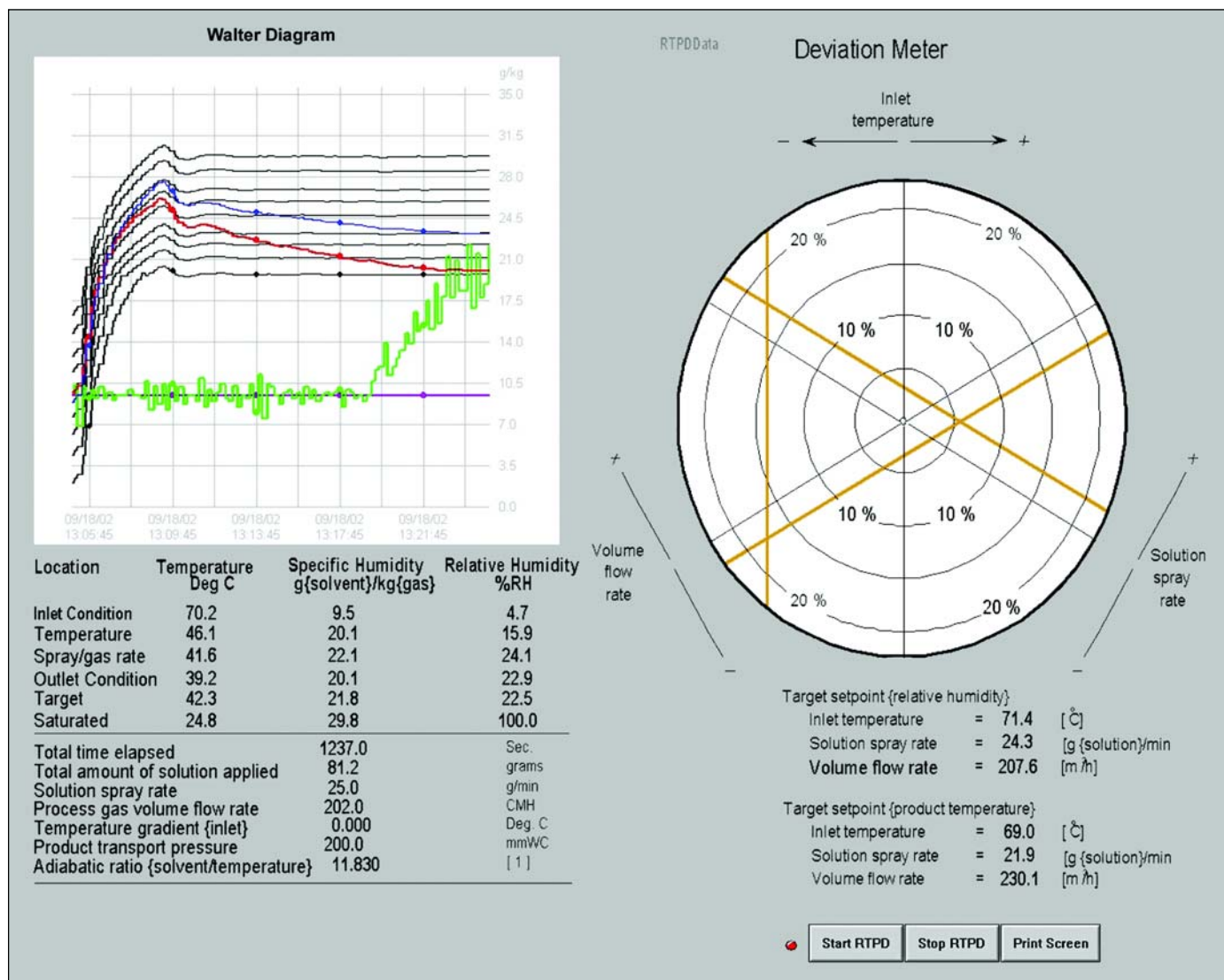


Figure 3. Thermodynamics process screen.

target process variables in both graphical and digital form - *Figure 3*. The deviation meter at the right shows that the inlet temperature (gold line) should be increased 15% to achieve the desired thermodynamic condition. Alternatively, the solution spray rate could be decreased less than five percent or the volume flow rate could be increased by less than five percent. Below the deviation meter are the calculated numerical target setpoints for inlet temperature, solution spray rate, and volume flow rate.

The current process values are given at the left side of the screen, below the graph. The inlet temperature is 70.2°C, and the deviation meter shows that a change of the inlet temperature to 71.4°C will give the desired relative humidity. Likewise a change in solution spray rate from the actual 25.0 g{solution}/min to the target 24.3 g{solution}/min will produce the desired condition. A third possibility is to change the volume flow rate from the current 202 m³/h to 207.6 m³/h.

The graph on the left side is the dynamic specific humidity diagram (Walter diagram). All the process values are calculated as the specific humidity along the adiabat that goes through the inlet condition. The violet line is the ambient condition, less than 10 g{water}/kg{air}, which is a dewpoint temperature of 14°C. The green line is the addition of water or solvent from the solution spray rate. Until 12 minutes ago, the green line was overlapping the violet line, which indicates that no spraying was occurring.

The black lines represent where the relative humidity values cross the constant enthalpy line or adiabat. The upper black line is the saturated humidity. The left side of the graph shows the specific humidity of the saturated line, which is approximately 16 g{water}/kg{air}. This indicates that 6 g{water}/kg{air} adiabatic could be added to the ambient gas before the gas would become saturated. The saturated line grows over the next four minutes to a specific humidity of 31 g{water}/kg{air} as the inlet temperature increases. The saturated line decreases when the inlet temperature passes the setpoint as the temperature controller begins to take over. The temperature under-shoots and reaches the final inlet temperature in less than four minutes. The other constant relative humidity lines parallel the saturated specific humidity line.

The red line represents the product temperature. The line has the same initial value as the violet line, which is the ambient condition. The inlet gas flow is cooled by the inlet duct and equipment plenum and delivers heat to the product. This is a non-adiabatic situation, because there is heat exchange with the surroundings. Initially, the product temperature is between the fourth and the fifth relative humidity line. As the heat is delivered to the equipment and product, the product temperature line decreases to the level of the ninth relative humidity line. If the relative humidity could be measured inside the process chamber, it would show a similar decrease during the elapsed time, real physical behavior.

The blue line represents a modified outlet temperature. Since the specific humidity of the outlet temperature is the same as the specific humidity of the product temperature, the two lines should overlap. So the outlet temperature line is modified by calculating the relative humidity of the outlet

temperature based on the cooling with constant specific humidity (the product specific humidity), providing information on the relative humidity in the outlet of the process chamber where the filter is located. In top spray granulation, the outlet temperature line indicates when the relative humidity is high at the filter, which can produce tacky product that will begin to block the filter. In bottom spray coating, the blue line can cross the red line, which means that the product temperature is lower than the outlet temperature. This occurs when the solvent is not totally evaporated from the coat during the free flight of the product, causing an increase of the solvent content in the product. The coat will become tacky and the product load will start to lump together, bringing the coating process to a standstill.

The graph shows that the spray pump was initiated eight minutes ago, because the specific humidity value increased, as shown by the increase of the green line. The difference between the violet line and the green line is the addition in specific humidity due to the spraying. It was observed that the red line (the product temperature) stops decreasing after the green line has reached the same specific humidity as the specific humidity of the product temperature.

The numerical values at the current condition are below the graph. The target relative humidity is 22.5%{saturated}, which will, together with the inlet temperature and the ambient specific humidity, give a product temperature of 42.3°C. We also can see the product temperature that will give a saturated condition, 24.8°C. The relative humidity based on the product temperature is 15.9%{saturated} and the outlet relative humidity is 22.9%{saturated}. The relative humidity created by the spraying is 24.1%{saturated}.

Finally, the lower left corner shows general process information, such as the time that has elapsed, the amount of solution delivered to the process and the current rate of spraying and process gas volume flow rate.

The product transport pressure is measured as the pressure difference between the empty equipment at the given volume flow rate and the current pressure loss over the equipment. With this value, it is possible to calculate how much product is moving around in the equipment, using the first law of thermodynamics, the conservation of enthalpy.

References

1. Ebey, G.C., "A Thermodynamic Model for Aqueous Film-Coating," *Pharmaceutical Technology*, (1987), April.
2. Okhamafe, A. O., and York, P., "Characterization of Moisture Interaction in Some Aqueous-Based Tablet Coating Formulations," *Journal of Pharmacy and Pharmacology*, (1985), pp. 37, 385-390.
3. Hyland, M., and Naunapper, D., Process Development Group, Goedecke, A.G., and Glatt, "Continuous Control of Product Moisture Content in Drying Process, Drug made in Germany," (1988), No. 1, p. 31.
4. Wantano, S., Hiroko, T., et. al, "Modeling Drug Release from Granule Coated with an Aqueous-Based System of Acrylate Methacrylate: Effect of Moisture Content on the Kinetics of Drug Release," *Chemical Pharmaceutical Bul-*

- letin*, (1994), 42(11) 2338-2341.
5. Watano, S., Kiyomi, Y., et al., "Evaluation of Aqueous Enteric Coated Granules Prepared by Moisture Control Method in Tumbling Fluidized Bed Process," *Chemical Pharmaceutical Bulletin*, (1994), 42(3).
 6. Watano, S., Ikuko, W., et al., "Modeling and Simulation of Drug Release from Granule Coated with Aqueous-Based System of Acrylic Copolymer," *Chemical Pharmaceutical Bulletin*, (1995), 43(5).
 7. Walter, K., "Real Time Process Determination to Achieve Reproducible Coating Results," Proceedings Second European Coating Symposium, (1997), 227-235.
 8. Walter, K., "A New Method of Controlling the Process Humidity when Coating Particulars," Proceedings Fifth European Coating Symposium, (2003), 82-87.
 9. Larsen, C. C., Holm, P., et. al., "A New Process Control Strategy for Aqueous Film Coating of Pellets in Fluidized Bed," *European Journal of Pharmaceutical Sciences*, (2003), 20, 273-283.

Note: Real Time Process Determination is a trademark of Niro Inc.

About the Author



Kim Walter acquired a Bachelors degree in machine-engineering in 1968. After serving in the Danish Royal Air Force, he earned a Masters degree in machine-engineering and a PhD from the Department of Fluid Mechanics at the Technical University of Denmark in Copenhagen, (former DTH). Throughout his career, he has combined inventiveness and computer programming, beginning with his first invention in noise control and a PhD project that developed

a calculation to determine flow around blunt objects using a laser doppler anemometer. He has been with GEA Niro since 1978, beginning as scientist/researcher at Niro Atomizer A/S in Copenhagen, where he worked on kiln technology and patented a new kiln design. In 1991, he became a senior technical advisor responsible for process equipment for the pharmaceutical industry, designing and patenting new equipment - precision coater, roto-processor, precision granulator, and tablet coater. He also developed a new control philosophy, real time process determination, commercially used since 2001. He is now a Senior Process Engineer at Niro Inc., USA, where he is an expert in coating technique and equipment, developing sophisticated and proprietary process technology and building up a technology center used by GEA Niro worldwide. He has numerous patents and published articles. He can be contacted by e-mail at: kw@niroinc.com.

Niro Pharma Systems, 9165 Rumsey Rd., Columbia, Maryland 21045. 