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SCALE-UP OF A SPRAY DRY TABLET GRANULATION PROCESS: THERMODYNAMIC CONSIDERATIONS

J. Berman, P. Pierce and P. E. Page
Marion Merrell Dow Inc., Kansas City, MO 64137.

ABSTRACT

An aqueous solution of a drug and binder is spray dried and subsequently compressed into tablets. A macroscopic, steady-state application of the Laws of Conservation of Mass and Energy is used to facilitate the scale-up of this continuous granulation process. The resulting equation describes the spray rate (throughput) of the feed solution as a function of: (i) the product of the temperature drop across the spray dryer and the mass flow rate of bone-dry air through the system, (ii) the temperature of the exhaust air, (iii) the absolute humidity of the inlet air, (iv) the overall thermal conductance of the system and (v) the thermophysical properties of the feed solution. This theoretical equation compares favorably to experimental data collected from pilot and production scale processes. Independent variation of the process variables in the model demonstrates that the first parameter is the primary determinant of spray rate. This thermodynamic analysis provides a bridge between processes of different scales. It is considerably more powerful than a series of experiments performed at discrete scales. These results are used in conjunction with equilibrium moisture, tabletting and other experimental data to suggest a rational approach to process scale-up and optimization.

INTRODUCTION

Spray drying is a process that enjoys widespread acceptance in the food, chemical and pharmaceutical industries. Many familiar products such as powdered milk, detergents and some pharmaceutical materials are manufactured in this manner. Since spray drying profoundly modifies the physical properties of certain substances it can provide an appealing alternative to conventional methods of wet granulation that are used for pharmaceutical products. In the areas of process control, product consistency, scale-up and validation the continuous spray drying process offers many practical advantages over batch granulation techniques. Excellent comprehensive reviews of spray drying in general (1) and of pharmaceuticals (2) in particular appear in the literature. The purpose of this work is to suggest a rational approach to process scale-up based on thermodynamic considerations.

As an example, consider the case of drug DG. DG is formulated as an instant release tablet of relatively high strength. This substance is non-hygroscopic, freely soluble in water, incompatible with many common pharmaceutical excipients and exhibits poor flow and compactibility. DG tablets produced using high shear wet granulation methods are relatively large. This problem is resolved by using a spray dry granulation process. Spray drying allows preparation of DG tablets that contain a minimum quantity of excipient.

A flow diagram of the spray drying process is presented in FIGURE 1. In this operation an aqueous feed solution, consisting of DG and a small quantity of binder, is pumped continuously through a rotary atomizer located at the top of a cylindrical chamber. The atomized droplets are convected downward by a stream of heated air. Water rapidly evaporates from the droplets as a result of simultaneous heat and mass transfer. There are two exit streams from the spray dryer. The first stream contains dried spherical particles that consist of DG and binder. The second stream is comprised of cooled humidified air. The physical properties of DG make it particularly amenable to spray drying.

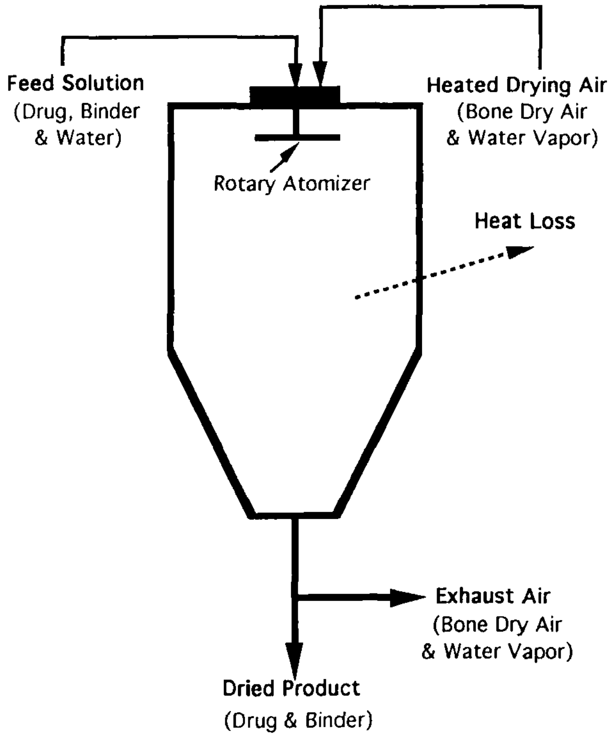

FIGURE 1
Schematic of the Spray Drying Process

The profound effect that this process has on the morphology of the material is vividly illustrated in FIGURES 2 and 3. FIGURE 2 is a photomicrograph of the drug substance. DG's poor flow properties are clearly derived from its morphology. The spray dried powder (refer to FIGURE 3), on the other hand, exhibits excellent flow due to the spherical nature of its particles. The feed solution provides intimate contact between DG and binder which leads to significantly enhanced compactibility. After lubrication, the spray dried powder can be directly compressed into tablets. These tablets, which contain DG in excess of 96% (wt/wt), exhibit excellent weight variation, hardness, friability, and dissolution. Furthermore, since the inlet stream is a solution, the formulation and process are protected from variations in

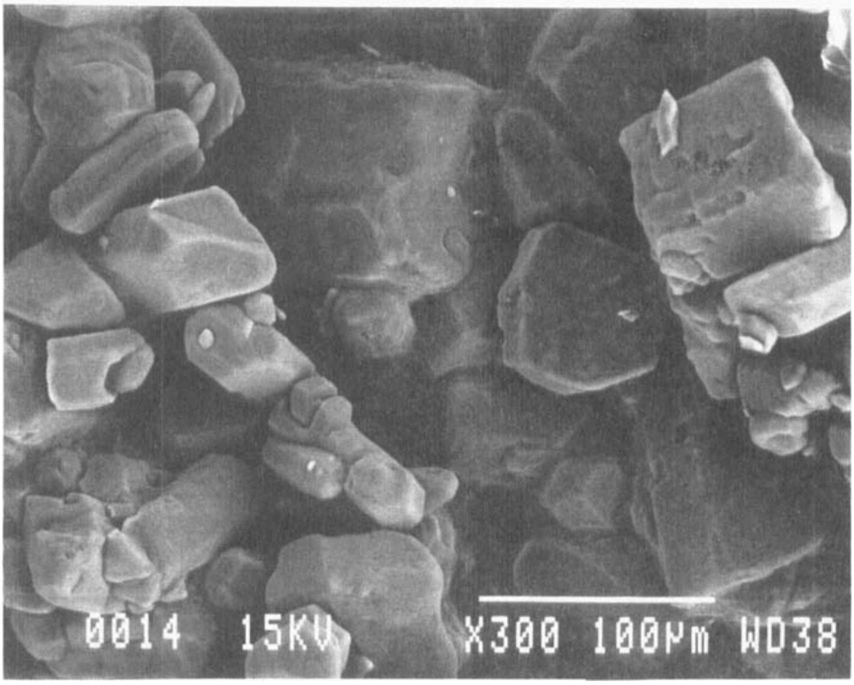

FIGURE 2
Scanning Electron Micrograph of the Drug Substance
(300X Magnification)

the physical properties of the drug substance, such as particle size and shape, which normally occur during development. These considerations, plus the fact that the process is independent of batch size, significantly simplify scale-up and validation.

THEORY

In practice, the inlet air to the spray dryer is heated to a particular temperature and the spray (feed) rate of the solution is adjusted to maintain a fixed outlet (exhaust) temperature, humidity or product moisture content. The exhaust temperature (humidity) must be high (low) enough to insure proper drying of the product. Since these

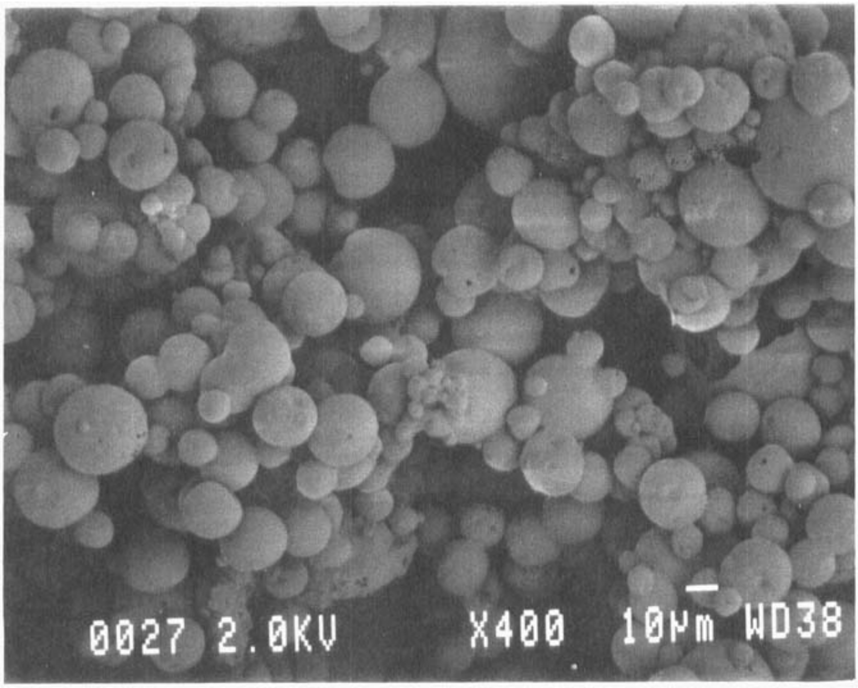

FIGURE 3
Scanning Electron Micrograph of the Spray Dried Powder
(400X Magnification)

conditions can influence the physical properties of the product it is important that they are properly controlled. A thermodynamic analysis greatly enhances the ability to predict, control and understand the process, particularly during scale-up.

In this section, an equation that characterizes the spray rate as a function of the critical process parameters is developed. This is accomplished by applying the Laws of Conservation of Mass and Energy (First Law of Thermodynamics) to this continuous process. The resulting equation provides a method, independent of process scale, for predicting and controlling the process outlet streams and hence, in part, the quality of the product.

As in any mathematical model, certain fundamental assumptions are necessary to simplify the analysis. The key assumptions and simplifications employed in this analysis are: (a) the control volume for this open system coincides with the walls of the spray dryer (refer to FIGURE 1), (b) the process is at steady state, i.e. the inlet and outlet streams are constant, (c) the product is thoroughly dried, i.e. it contains no moisture, (d) the ambient temperature surrounding the spray dryer is constant at ~22°C, (e) the change in enthalpy of the feed solution is approximated by the sum of the changes in enthalpy of the solutes and solvent, (f) the dried powder exits the spray dryer at ~60°C, (g) the presence of binder does not contribute to the energy (of mixing) associated with the feed solution and (h) adequate accuracy is provided by averaging specific heat capacities over the temperature range of interest.

With these assumptions the First Law of Thermodynamics for the system represented in FIGURE 1 specifies that "the rate at which energy enters the system via all of its inlet streams is equal to the rate at which it leaves via all of its outlet streams plus the rate at which energy is lost from the system in the form of heat".

Heat is lost from the spray dryer primarily through its "seams" and, to a much lesser extent, through its insulated walls. The average flux of heat lost through the boundaries of the spray dryer is characterized by the overall heat transfer coefficient. In general, this coefficient is an all encompassing parameter that takes into account the geometry, fluid mechanics and the thermophysical properties of the system. The rate at which heat is lost from the process is calculated from an expression analogous to Newton's Law of Cooling (refer to the NOMENCLATURE section for a description of the symbols):

$$Q_l = UA(T_o - T_r). \quad [1]$$

The mathematical statement of the First Law of Thermodynamics for this open system is:

$$\Sigma(m\ h)_{\substack{\text{inlet}\\ \text{streams}}} = \Sigma(m\ h)_{\substack{\text{outlet}\\ \text{streams}}} + UA(T_o - T_r). \quad [2]$$

The inlet energy streams,

$$\sum(\mathrm{m\ h})_{\substack{\mathrm{inlet}\\ \mathrm{streams}}} = [\mathrm{m_a\ h_{ai}} + \mathrm{m\hat{v}\ h_{vi}}] + (\mathrm{m_s\ h_{sf}}), \qquad [3]$$

consist of the drying air (the terms that appear within the [ ] in equation [3]) and the feed solution. The drying air contains both bone-dry air (BDA) and water vapor. Similarly, the outlet energy streams,

$$\sum(\mathrm{m\ h})_{\substack{\mathrm{outlet}\\ \mathrm{streams}}} = [\mathrm{m_a\ h_{ao}} + \mathrm{m\hat{v}\ h_{vo}} + \mathrm{x_w\ m_s\ h_{vo}}] + (\mathrm{x_d} + \mathrm{x_b})\mathrm{m_s\ h_{pe}}, \qquad [4]$$

consist of the humidified exhaust air (the terms that appear within the [ ] in equation [4]) and the spray dried product. The moisture in the exhaust air is derived from the water vapor that entered the system in the drying air plus the water that evaporated from the feed solution (the last term in the [ ] in equation [4]) as a result of the drying process. The overall energy balance is obtained by inserting equations [3] and [4] into equation [2], substituting the expression for absolute humidity of the inlet air ($\mathrm{W_i = m\hat{v}/m_a}$), and rearranging:

$$\begin{aligned} \mathrm{m_a}\ [(\mathrm{h_{ai}} - \mathrm{h_{ao}}) + \mathrm{W_i}(\mathrm{h_{vi}} - \mathrm{h_{vo}})] - \mathrm{UA}(\mathrm{T_o} - \mathrm{T_r}) \\ = [(\mathrm{x_d} + \mathrm{x_b})\ (\mathrm{m_s\ h_{pe}}) + (\mathrm{x_w\ m_s\ h_{vo}})] - \mathrm{m_s\ h_{sf}}. \end{aligned} \qquad [5]$$

The next step in the analysis is to substitute specific thermodynamic relationships into equation [5] that will allow calculation of enthalpy changes from measurable quantities. These relationships are readily found in the literature for both water and BDA. The change in specific enthalpy, between two states, is calculated by integrating the specific heat capacity of the species over the temperature range that separates the two states. In general, the specific heat capacity is a function of temperature, however, the analysis can be simplified without significantly compromising its accuracy by utilizing a mean heat capacity. The mean heat capacity is constant over the temperature range of interest, thus:

$$\Delta \mathrm{h} = \mathrm{hi} - \mathrm{ho} = \int_{\mathrm{To}}^{\mathrm{Ti}} \mathrm{C}\ [\mathrm{T}]\ \mathrm{dT} \approx \int_{\mathrm{To}}^{\mathrm{Ti}} \overline{\mathrm{C}}\ \mathrm{dT} = \overline{\mathrm{C}}\ (\mathrm{Ti} - \mathrm{To}), \qquad [6]$$

in which:

$$\overline{\mathrm{C}} = \left\{\int_{\mathrm{To}}^{\mathrm{Ti}} \mathrm{C}\ [\mathrm{T}]\ \mathrm{dT}\right\} \Big/ \left\{\int_{\mathrm{To}}^{\mathrm{Ti}} \mathrm{dT}\right\}. \qquad [7]$$

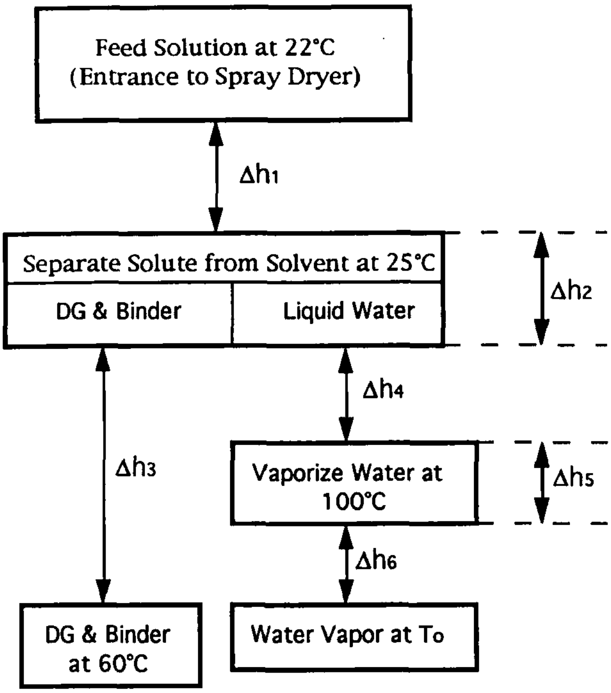

FIGURE 4
Heat Effects Associated With Spray Drying of Feed Solution
(Not Drawn to Scale)

For air [$\bar{C}_a$ = 1.02 KJ/Kg/°C between 60°C and 230°C (**3**)]:

$$\Delta h = h_{ai} - h_{ao} = \int_{T_o}^{T_i} 1.02\, dT = 1.02\,(T_i - T_o). \qquad [8]$$

Similarly, the change in specific enthalpy of the water that entered the spray dryer as vapor is written [$\bar{C}_v$ = 1.92 KJ/Kg/°C between 60°C and 230°C (**3**)] as:

$$\Delta h = h_{vi} - h_{vo} = \int_{T_o}^{T_i} 1.92\, dT = 1.92\,(T_i - T_o). \qquad [9]$$

The right hand side of equation [5] characterizes the change in enthalpy of the feed material between its inlet and outlet states. Since specific enthalpy is a state property, this change may be calculated by devising any path which takes an aqueous solution of DG and binder, of fixed concentration, at 22°C to a dry powder at 60°C and pure water vapor at T_o. It is convenient to devise a path that takes advantage of existing or readily measured thermal parameters for the system. One such path is illustrated in FIGURE 4. In this path, the overall process is divided into six sub-processes; the total energy change is the sum of the heat effects associated with each of the six steps:

$$[(x_d + x_b)(m_s h_{pe}) + (x_w m_s h_{vo})] - m_s h_{sf} = m_s \sum_{n=1}^{6} \Delta h n. \qquad [10]$$

In the first step, the temperature of the feed solution is increased from its inlet state of 22°C to 25°C. This change is approximated as the sum of the enthalpy changes of the solute and solvent. The heat capacity of a solid mixture of DG and binder ($y_d = 0.97$ and $y_b = 0.03$) over this narrow temperature range is essentially constant at 1.32 KJ/Kg/°C (measured with a Perkin-Elmer DSC-7 Differential Scanning Calorimeter). The heat capacity of liquid water is constant at 4.19 KJ/Kg/°C **(3)**, thus (note: $x_d + x_b + x_w = 1$):

$$\Delta h_1 \approx [3.96\,(1 - x_w) + 12.6\, x_w]. \qquad [11]$$

In the second step, the liquid water is separated from the product at 25°C. The heat of mixing associated with the preparation of an aqueous solution of DG at x_d and ~25°C is 242 KJ/Kg of DG (measured with a Setaram C-80 calorimeter). The energy necessary to separate DG from water at this temperature is the negative of this quantity. It is assumed that the heat of mixing associated with the small quantity of binder employed in this formulation is negligible. Thus:

$$\Delta h_2 \approx (-242)(1 - x_w). \qquad [12]$$

Equation [12] is an accurate approximation as long as the concentration of DG in the feed solution does not vary significantly from x_d; it is obviously precise in the limit of $x_w = 1$.

In the third step, the temperature of the solutes is increased from 25°C to their exit state of ~60°C. The average heat capacity of a solid mixture of DG and binder ($y_d = 0.97$ and $y_b = 0.03$) over this temperature range is calculated from calorimetry measurements to be 1.37 KJ/Kg/°C. Thus:

$$\Delta h_3 = 48.0(1 - x_w). \qquad [13]$$

In the fourth step, the temperature of the solvent (i.e. liquid water) is increased from 25°C to 100°C:

$$\Delta h_4 = (314)x_w. \qquad [14]$$

In the fifth step, the liquid water is completely vaporized at 100°C. The heat of vaporization of water at this temperature is 2257 KJ/Kg **(3)**, thus:

$$\Delta h_5 = (2257)x_w. \qquad [15]$$

In the final step, the temperature of the water vapor is changed from 100°C to the exhaust temperature of the air:

$$\Delta h_6 = [1.92\ (T_o - 100)]\ x_w. \qquad [16]$$

Substituting these expressions for the enthalpy changes of the process streams, equations [8] - [16], into the overall energy balance, equation [5], leads to the following expression for the spray rate:

$$m_s = \frac{[(T_i - T_o)(m_a)(1.02 + 1.92\ W_i) - UA\ (T_o - 22)]}{[(190)(x_w - 1) + x_w\ (1.92\ T_o + 2390)]}. \qquad [17]$$

Based on the simplifying assumptions of this analysis, equation [17] indicates that the spray rate is a function of (i) the product of the temperature drop across the spray dryer and the mass flow rate of bone-dry air through the system, (ii) the temperature of the exhaust air, (iii) the absolute humidity of the inlet air, (iv) the overall thermal conductance (UA) of the system and (v) the thermophysical properties of the feed solution:

$$m_s = f\,[(T_i - T_o)\ m_a,\ T_o,\ W_i;\ UA,\ \text{thermal properties}]. \qquad [18]$$

Equation [17] provides a method for calculating the spray rate (throughput) as a function of these critical process parameters. It is independent of the scale of the equipment and applies to any process for DG at x_d that can be represented by FIGURES 1 and 4.

Process optimization and scale-up can be facilitated by understanding the affect of the critical process parameters on spray rate and exhaust humidity. The accuracy and utility of equation [17] is assessed by comparing its predictions to experimental data.

EXPERIMENTAL METHODS

Aqueous solutions of DG and binder were spray dried using pilot and production scale equipment manufactured by Niro Atomizer Inc. (Copenhagen, Denmark). These units are geometrically similar and employ rotary atomization with co-current flow of feed and air. They consist of a vertical cylindrical chamber that is stacked on top of a 60° right cylindrical cone. The pilot scale model is a Niro type HT portable spray dryer equipped with two point (chamber and cyclone) product discharge. It is instrumented so that the temperature, dew point and the flow rate of the ambient inlet air can be measured with a Hygro-Thermometer Anemometer (Omega, model HHF710, Stamford, CT) attached to the inlet air port. The production scale spray dryer is a custom built unit that is owned by an ethical pharmaceutical company; spray dry granulation of DG was conducted as part of its third party manufacturing program. This dryer is equipped with a pneumatic product collection system but is not instrumented to control or measure the humidity of the inlet ambient air. The key dimensions and features of the pilot and production scale spray dryers are presented in TABLE 1.

A series of statistically designed experiments was conducted at the pilot scale. In these experiments, the composition of the feed solution, heated inlet air temperature and atomizer speed were methodically varied and the spray rate was adjusted to achieve a targeted exhaust temperature (or humidity). At the beginning of an experiment, steady state operation at the desired inlet and exhaust conditions was first achieved using deionized water as the feed. The feed was then switched to the DG/binder solution of interest and the spray rate was adjusted in order to maintain the desired exhaust temperature (or humidity). The HT spray dryer was always operated with its air flow control damper fully open (maximum air flow). The spray dried granulation was subsequently compressed into tablets after adding small quantities of glidant and lubricant. Various analyses were performed on the granulation and resulting tablets.

Due to practical constraints, the production scale runs were limited to two separate but similar campaigns. The procedures used with

TABLE 1

Critical Dimensions of Pilot and Production Scale Spray Dryers

PARAMETERS	PILOT SCALE	PRODUCTION SCALE
Diameter [m]	0.80	3.05
Height of Cylindrical Section, [m]	0.60	3.05
Surface Area, A, [m^2]	3.0	47.9
Volume, V, [m^3]	0.42	26.7
Maximum T_i, [°C]	350	240
Nominal Mass Flow Rate of Drying Air, [Kg air/hr]	~90	~2300
Rotary Atomizer - Type	24 Vane	24 Hi Vane
Atomizer Height, [mm]	6	22
Atomizer Diameter, [cm]	5	12
Normal Atomizer Operating Speed, [rpm]	20,000-32,000	20,000

this unit were generally the same as those described for the pilot scale device although the humidity of the inlet ambient process air was not measured in either of these two campaigns.

RESULTS

The utility of equation [17] can be assessed by comparing it to experimental data collected at pilot and production scales. In order to perform this assessment it is necessary to secure an estimate of U, the overall heat transfer coefficient, for each spray dryer. Unfortunately, these quantities are not available from the equipment manufacturer. They can, however, be approximated from data collected with water (the feed during the start-up of the spray drying experiments) and equation [17]. In this method the measured values of T_o, T_i, W_i, m_a and

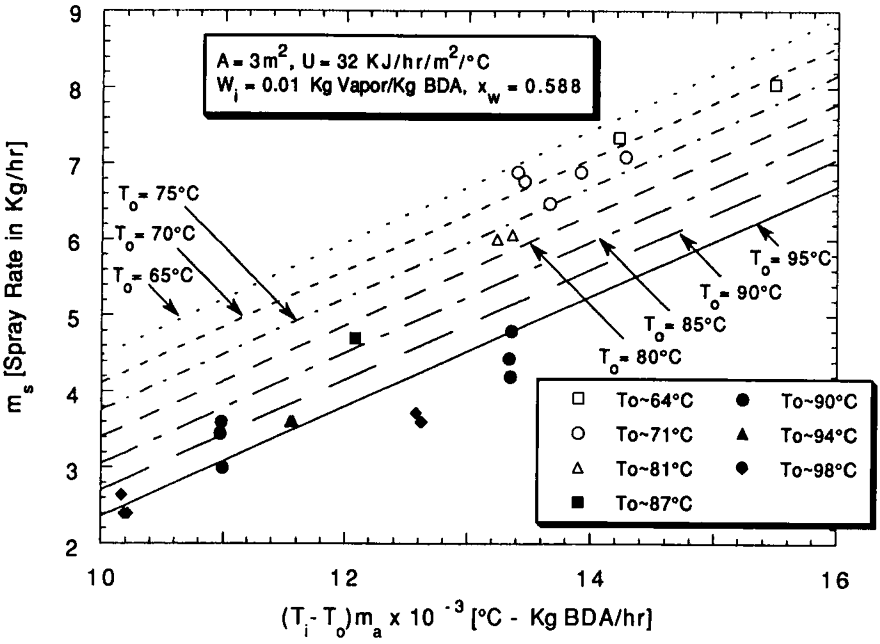

FIGURE 5
Theoretical Predictions (Equation [17]) and Experimental Measurements for the Pilot Spray Dryer

m_s (for $x_w = 1$) are inserted into equation [17] which is then solved for U.

Using this technique the average overall heat transfer coefficient for the pilot spray dryer is estimated to be 32 KJ/hr/m^2/°C (n = 11, SD = 3.4). The theoretical spray rates described by equation [17] are plotted as a function of [$(T_i - T_o)\, m_a$], in FIGURE 5, for this spray dryer. These curves were generated with $W_i = 0.01$ Kg water vapor/Kg BDA, $x_w = 0.588$, U = 32 KJ/hr/m^2/°C and T_o = 65°C, 70°C, 75°C, 80°C, 85°C, 90°C and 95°C. Experimental data collected at exhaust temperatures of roughly 64°C, 71°C, 81°C, 87°C, 90°C, 94°C and 98°C are also included in this figure. These data cover experimental conditions for W_i ranging from 0.007 to 0.011 Kg water vapor/Kg BDA (median = 0.01) and for x_w ranging from 0.575 to 0.596 (median = 0.588). The data compare favorably with the

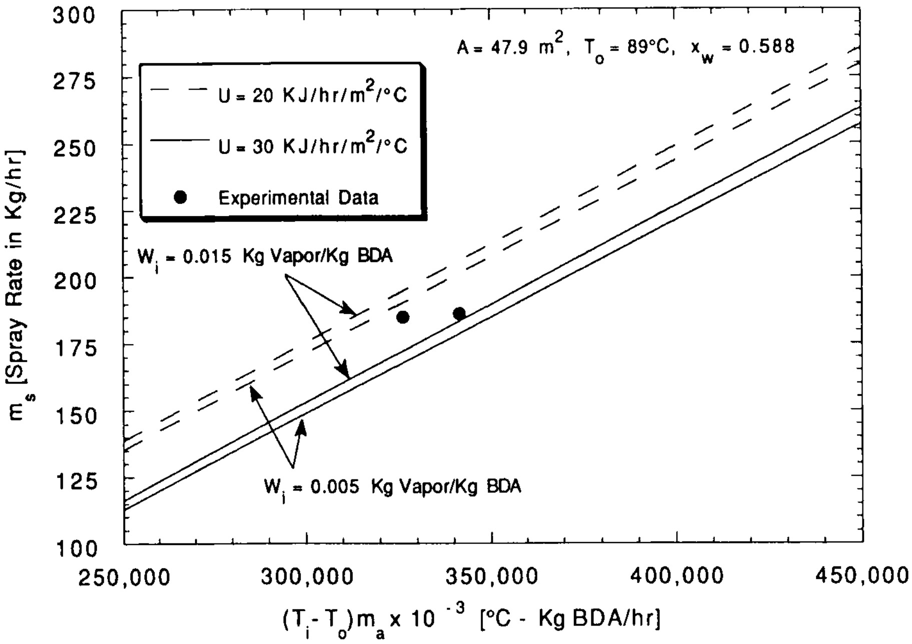

FIGURE 6

Theoretical Predictions (Equation [17]) and Experimental Measurements for the Production Spray Dryer

theoretical solution. These results indicate that spray rate increases primarily with increasing $[(T_i - T_o)\, m_a]$ and, to a lesser extent, with decreasing T_o.

Due to practical constraints, only limited experimental data have been generated at the production scale. This makes it difficult to secure a reliable estimate of U for the larger unit and requires an alternative approach to the method outlined above. FIGURE 6 shows the spray rates in the production scale spray dryer as a function of $[(T_i - T_o)\, m_a]$. Included in this figure are data from two production runs ($T_o = 89°C$, $x_w = 0.588$) and four theoretical curves generated with equation [17]. These curves show how changes in inlet humidity ($W_i = 0.005$ and 0.015 Kg water vapor/Kg BDA) and the overall heat transfer coefficient ($U = 20$ and 30 KJ/hr/m^2/°C) affect the spray rate. The range of inlet humidities was chosen to bracket those measured during the pilot scale experiments and is relatively wide. The two values of U were chosen so that the theoretical curves of FIGURE 6 bracket the experimental data. In this manner, an estimate of the overall heat transfer coefficient can be obtained, which in turn is a rough measure of heat loss for a particular set of operating conditions.

These analyses suggest that the overall heat transfer coefficient of the production scale spray dryer ($A = 47.9\ m^2$, $U \sim 25\ KJ/hr/m^2/°C$) is approximately 20% less than that of the pilot unit ($A = 3\ m^2$, $U \sim 32\ KJ/hr/m^2/°C$). These estimates are qualitatively reasonable since a larger fraction of the pilot unit's boundaries (i.e. surface area) is comprised of gaskets, site ports and other non-insulated areas where appreciable heat loss can occur. These estimates are also consistent with the range of overall heat transfer coefficients, 8.4 - 29 $KJ/hr/m^2/°C$, reported in the literature (1) for very large industrial spray dryers.

Equation [17] and FIGURES 5 and 6 are mathematical and graphical statements of the Laws of Conservation of Mass and Energy for this process. They indicate that the spray rate is primarily determined by the parameter $[(T_i - T_o)\ m_a]$. The spray rate must increase with $[(T_i - T_o)\ m_a]$ in order to maintain a balanced process (or alternately $[(T_i - T_o)\ m_a]$ must increase if the spray rate is increased). This parameter is a measure of the evaporative capacity of the process which can be modified by adjusting m_a and/or $(T_i - T_o)$. The maximum value of m_a is determined by the scale of the equipment. With the exception of hard to dry products, spray dryers are usually operated at the highest m_a in order to achieve maximum throughput and process economy. A significant increase in m_a can only be achieved by changing equipment.

The range of attainable inlet temperatures is dictated by equipment and energy constraints. Unlike m_a, it is usually possible to achieve higher inlet temperatures with smaller scale equipment. The actual T_i used in a process is primarily determined by the temperature sensitivity of the product. The temperature of the exhaust air is raised (or lowered) by decreasing (or increasing) the spray rate. Increasing the spray rate results in greater evaporative cooling (assuming the drying air remains below its saturation point) which leads to lower exhaust temperatures. In practice, m_a and T_i are set to prescribed levels and the spray rate is used to control T_o and hence $[(T_i - T_o)\ m_a]$.

The exhaust temperature also appears independently of $[(T_i - T_o)\ m_a]$ in equation [17]; T_o is a secondary determinant of spray rate. FIGURE 5 shows, for fixed $[(T_i - T_o)\ m_a]$, that higher spray rates can be achieved by operating at lower exhaust temperatures. This effect is primarily related to heat loss from the system. Equation [1] indicates that the rate at which heat is lost decreases as the exhaust temperature decreases. As this occurs more energy becomes available for evaporative purposes and the spray rate must increase in order to keep the process in balance. In a perfectly insulated system (i.e. U = 0) the exhaust temperature has a negligible affect on spray rate.

The rate at which heat is lost from a spray dryer is proportional to UA, its thermal conductance. In general, as you go up in scale, surface area increases faster than U decreases and the rate of heat loss becomes more appreciable. For example, under similar operating conditions, the production scale spray dryer (UA ~ 1198 KJ/hr/°C) probably loses heat at ~12.5 times the rate of the pilot scale unit (UA ~ 96 KJ/hr/°C). Despite this, the effect of heat loss on spray rate is less significant in the production unit. This is because the quantity of heat that is lost is a smaller fraction of the overall energy associated with the process. In other words there is more energy available to lose. The per cent decrease in spray rate that is attributable to heat loss may be calculated from equation [17]:

$$\begin{array}{c}\text{\% Decrease in Spray Rate} \\ \text{Due to Heat Loss}\end{array} = \frac{U\,A\,(T_o - 22)}{(m_a)\,(T_i - T_o)\,(1.02 + W_i)}. \qquad [19]$$

Equation [19] indicates that for fixed temperature and humidity the effect of heat loss on spray rate is proportional to (UA/m_a). For the most part, this parameter is a function of the spray dryer and not its operating conditions (spray dryers are usually operated at full throttle for easily dried products).

FIGURE 7 shows the per cent decrease in spray rate due to heat loss as a function of $[(T_i - T_o)\ m_a]$ (i.e. equation [19]) for $W_i = 0.01$ Kg

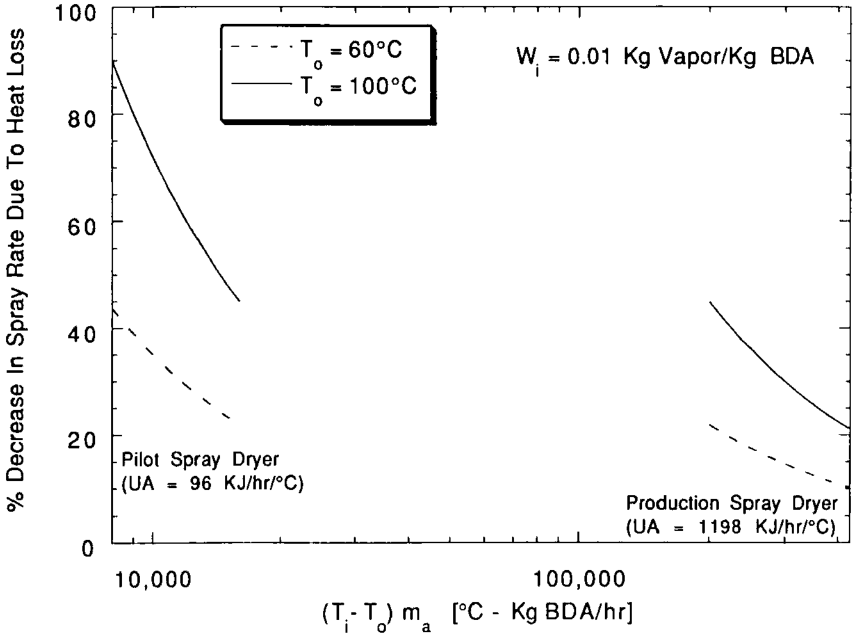

FIGURE 7

The Effect of Heat Loss on Spray Rate

water vapor/Kg BDA. Individual curves are presented for exhaust temperatures of 60°C and 100°C which bracket the limits of practical significance for this product. Also included in this figure are separate solutions for the pilot and production spray dryers which cover their appropriate ranges of operation. FIGURE 7 indicates that heat loss can have a profound effect on spray rate, particularly in smaller scale equipment. Depending on the operating conditions the decrease in spray rate due to heat loss will be 20 - 90% in the pilot spray dryer and roughly half this amount in the production unit.

The minor effect that inlet humidity has on spray rate is illustrated in FIGURE 6 for the production spray dryer. As W_i decreases the driving force for heat transfer increases and evaporative cooling becomes more pronounced. As a result, the spray rate must be decreased to prevent T_o from falling below its prescribed level. On the other hand, as W_i increases the spray rate must also increase so that T_o does not rise above this level. This does not suggest that it is desirable to raise the inlet humidity of the drying air in order to increase spray rate and process economy. On the contrary, it is best to maintain as low an inlet humidity as possible in order to insure adequate drying of the product and proper control of the process.

The reason for spray dry granulating a freely water soluble substance is to enhance its flow and compactibility. In order to accomplish this it is necessary to control the humidity of the exhaust air. An excessively high exhaust humidity can have a negative impact on drying, flow and/or stability. A low exhaust humidity, on the other hand, can lead to over drying. Thus, the exhaust humidity is a critical process control parameter. Unfortunately, it is difficult to reliably measure W_o due to the propensity for product to foul inline humidity probes. As an alternative to direct measurement we can estimate W_o by applying the Principle of Conservation of Mass. The absolute humidity of the exhaust air is a function of the absolute humidity of the inlet air and the amount of water evaporated during the process:

$$W_o = (m\hat{v} + x_w m_s)/m_a = W_i + (x_w m_s/m_a). \qquad [20]$$

The most accurate estimate of W_o is obtained by inserting measured values of W_i, x_w, m_s and m_a into equation [20]. In the absence of experimental data, W_o can be predicted by using equation [20] in conjunction with equation [17].

It is frequently more convenient to work with relative humidity rather than absolute humidity. Absolute humidity is defined as:

$$W = 0.621\ P^\circ/(P-P^\circ), \qquad [21]$$

whereas the per cent relative humidity at a particular temperature is:

$$\%RH = 100\%\ P^\circ/P^*(T). \qquad [22]$$

FIGURE 8 shows the per cent relative humidity of the exhaust stream of both the pilot and production scale equipment as a function of T_o for spray dried solutions of DG. These curves apply to fixed inlet temperature, humidity and concentration of feed solution. They were generated by: (i) using equations [17] and [20] to predict W_o,

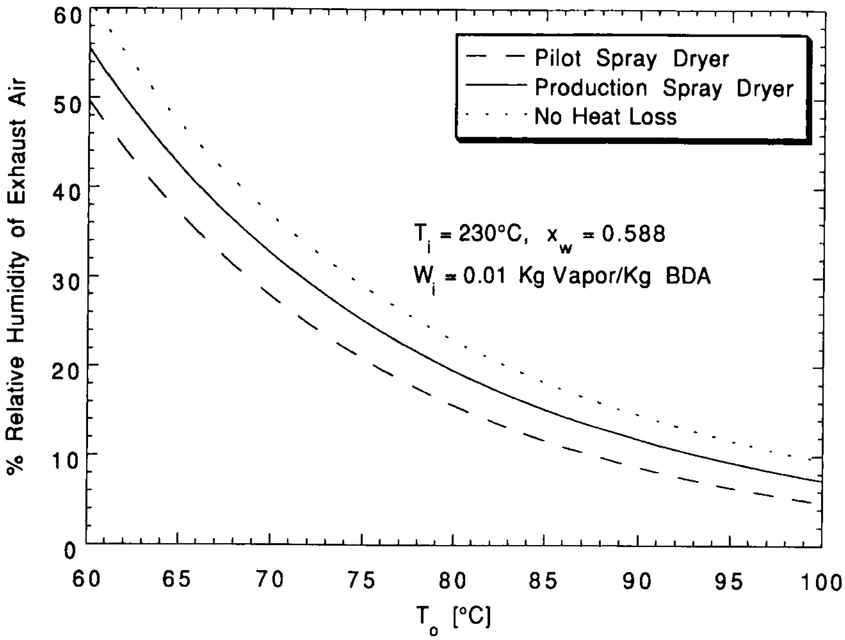

FIGURE 8

Predicted Per Cent Relative Humidity of Exhaust Air

(ii) solving equation [21] for P°, (iii) determining the vapor pressure of water at T_O using an inverted form of the Antoine Equation **(3)**:

$$P*(T_O) = 10^{\left\{7.96681 - \left[1668.21 / (T_O + 228)\right]\right\}} \qquad [23]$$

and (iv) calculating per cent relative humidity with equation [22]. The difference between the pilot and production scale curves of FIGURE 8 is due to heat loss. FIGURE 8 indicates that under similar operating conditions the exhaust humidity will be higher in the larger scale equipment. Thus, the exhaust humidity, not the exhaust temperature, should be used to control the spray dry granulation process. In the absence of heat loss the relative humidity of the exhaust is independent of the scale of the equipment; this solution is also presented in FIGURE 8. Although relatively large variations in humidity have only a minor effect on spray rate even small changes can have a profound impact on the quality of the product. The sensitivity of the physical properties of the spray dried powder to variations in humidity should be assessed prior to scale-up.

DISCUSSION

Spray drying can be a simple, effective and inexpensive method of enhancing the compactibility and flow of many water soluble drugs. There are many ways to assess the suitability of a new drug candidate for spray dry granulation. Initial experiments should focus on quantifying the equilibrium moisture content of the drug as a function of relative humidity (4). These experiments will determine the hygroscopicity of the drug and help to identify the optimum drying conditions for the process. Before proceeding we recommend performing a series of small scale, statistically designed experiments to determine the optimum composition of the feed solution.

One approach is to tray or vacuum dry aqueous solutions of drug and different binders at various concentrations. The macroscopic physical properties of the resulting powders or films should be assessed and their compaction properties analyzed using a single station tablet press. In general, the ideal formulation will contain the highest concentration of drug and the lowest concentration of binder and will produce a non-tacky easily dried powder that is highly compactible.

The next step in the development program is to perform a few screening experiments in a pilot scale spray dryer. The overall heat transfer coefficient for this spray dryer should be approximated using the techniques described above before proceeding with this portion of the program. The spray dryer and atomizer should be geometrically similar to the ultimate production unit. In addition, it is important to fully understand the dust explosion properties of the drug substance before attempting to spray dry the material.

The purpose of these screening experiments is to identify target values for the critical processing parameters. These parameters include T_i, T_o (this will determine the exhaust humidity) and the atomization conditions. The inlet temperature is dictated in part by the temperature sensitivity of the product and by equipment constraints. In general, maximum spray rate and process economy will be achieved at the highest T_i. The exhaust temperature should be chosen to provide an acceptable exhaust humidity based on the results of the equilibrium moisture experiments. This exhaust temperature can be predicted by developing an equation similar to equation [17] for the feed solution of interest and then employing equations [20] through [23]. Finally, the conditions of atomization will depend on the atomizer. For a rotary atomizer the key variable will be angular velocity.

In practice, T_i and the conditions of atomization will be set at predetermined levels and the spray rate will be adjusted to provide the targeted T_o. It is important to monitor m_s, m_a, W_i, T_i, T_o and the atomizer variables throughout the course of each experiment. A more accurate estimate of the exhaust humidity can then be obtained using these measured parameters and equations [20] through [23]. The physical and chemical properties of the spray dried product should also be assessed. These studies should include particle size, bulk and tapped density, moisture content, degradation, crystal structure, microscopic examination of particle morphology and a qualitative assessment of the macroscopic properties of the material. The product must also be compressed with an instrumented tablet press and the resulting tablets assayed and analyzed for weight variation, compaction, friability, disintegration and dissolution. Finally, the experimental data should be compared to the predictions of the appropriate form of equation [17].

The initial screening experiments will determine if the drug substance is amenable to spray dry granulation. If appropriate, the next step in the development program should be a full or partial factorial experiment at the pilot scale. This experiment should be designed to study the effects of T_i, T_o (i.e. exhaust humidity) and atomization on the quality of the spray dried product and subsequent tablets. A statistical analysis of the resulting data will identify the optimum processing conditions for the compound. Finally, a limited number of experiments should be performed with a geometrically similar production unit to verify the results of the pilot scale

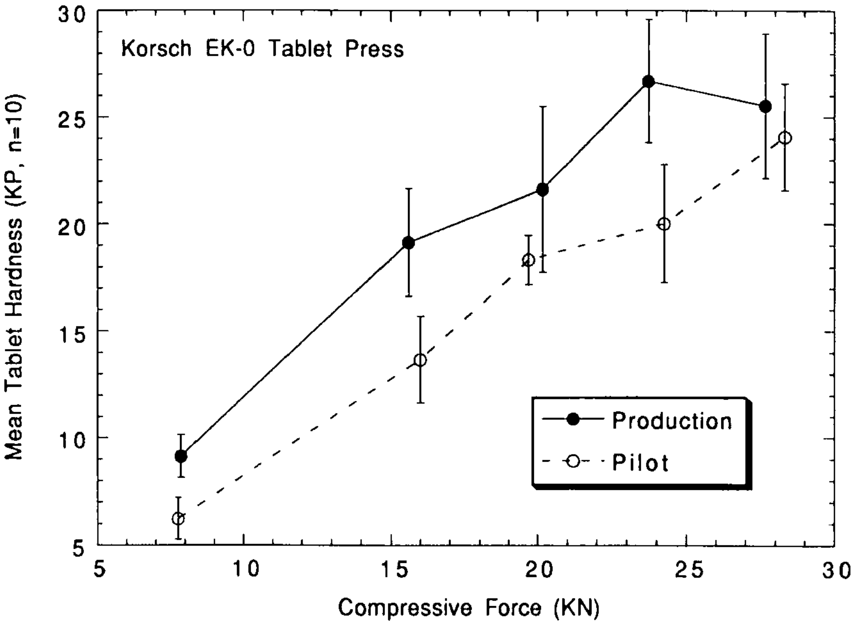

FIGURE 9

Compaction Profiles of Tablets Compressed from Spray Dried Granulation

experiments. The design of these scale-up experiments should incorporate many of the thermodynamic considerations presented in this work.

Drug DG has proven to be particularly amenable to spray dry granulation. Experiments at the pilot scale have demonstrated that the compactibility of the spray dried powder is dependent on the exhaust humidity. Data from a geometrically similar production dryer indicates that the process is readily scalable. As an example, FIGURE 9 shows the compactibility profiles (i.e. hardness vs. compression force) for tablets that were compressed (with a Korsch EK-0 instrumented tablet press) from material spray dried under similar conditions with pilot and production scale equipment. These profiles help to demonstrate the scalability of the process.

CONCLUSIONS

Spray drying can be used to significantly enhance the compactibility and flow of water soluble drug substances. This process enhances compactibility by providing intimate contact between drug and binder and enhances flow by producing spherical particles. By utilizing aqueous solutions the spray drying process is insulated from variations in the physical properties of the drug substance that can occur during product development. Spray drying also combines granulation and drying into one convenient unit operation. The continuous nature of this process makes it particularly conducive to scientific analysis and is more easily scaled-up, controlled and validated than conventional batch wet granulation techniques. The simplicity of the process can also help reduce valuable development time.

This work is an elementary application of the Laws of Conservation of Mass and Energy to the steady-state spray drying process; it is independent of process scale. The analysis indicates that spray rate is primarily determined by $[(T_i - T_o)\ m_a]$ although heat loss from the spray dryer to the surroundings can significantly effect the spray rate. In general, heat loss becomes less of a factor as the scale of equipment is increased. The humidity of the exhaust air from the spray dryer is a critical process control parameter. This humidity, which is a function of the mass flow rate and humidity of the process air and the rate at which water is evaporated during the process, can have a profound affect on the quality of the spray dried product. Equations are presented that can be used to predict or approximate the humidity of the exhaust air for a particular set of processing conditions.

The results of this analysis can be used to design an effective and efficient product development program. It is considerably more powerful than a purely empirical series of experiments. This analysis, however, by itself, will not predict the particle size distribution, density, moisture level or compactibility of the spray dried product. These properties will also depend on the atomization as well as the physical and chemical properties of the material which are not considered in this analysis. In the end, the most efficient and effective scale-up program will consist of both theoretical and experimental components which, after all, is the essence of the Scientific Method.

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NOMENCLATURE

A	Surface area of the spray dryer (system boundaries) $[m^2]$
C	Specific heat capacity [KJ/Kg/°C]
$\bar{C}$	Mean specific heat capacity [KJ/Kg/°C]
h	Specific enthalpy [KJ/Kg]
m_i	Mass flow rate of species i [Kg/hr]
P	Total pressure [mmHg]
P°	Partial pressure of water vapor [mmHg]
$P^*(T)$	Vapor Pressure of water at T [mmHg]
%RH	Per cent relative humidity
T	Temperature [°C]
Q_l	Rate of heat lost from spray dryer [KJ/hr]
U	Overall heat transfer coefficient $[KJ/hr/m^2/°C]$
W	Absolute humidity = m_v/m_a [Kg water vapor/Kg BDA]
x_i	Mass fraction of species i in feed solution [Kg /Kg solution]
y_i	Mass fraction of species i in spray dried powder [Kg/Kg]

Subscripts:

a	Bone-dry air [BDA]
b	Binder
d	Drug
e	State of product stream
f	State of feed solution stream
i	State of heated inlet air stream

o	State of outlet (exhaust) air stream
p	Product (i.e. spray dried powder)
r	Ambient state
s	Feed solution
v	Water vapor
$\hat{v}$	Water vapor that entered in inlet air stream
w	Liquid water

Symbols:

f	Function
Δ	Change in state

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