35

PROCESS DESIGN AND DEVELOPMENT FOR NOVEL PHARMACEUTICAL DOSAGE FORMS

LEAH APPEL, JOSHUA SHOCKEY, AND MATTHEW SHAFFER
Green Ridge Consulting, Bend, OR, USA

JENNIFER CHU
Pharmaceutical Sciences, Neurogen Corporation, Branford, CT, USA

35.1 INTRODUCTION

Strong fundamental knowledge of the formulation and process that is used for a pharmaceutical product is critical to ensuring efficacy, safety, and robust product quality. The design and development approach that is generally advocated in the pharmaceutical industry is called "quality by design" (QbD). This is the application of a scientifically logical approach to developing a formulation and process that is robust, well understood, and well characterized. Knowledge of science and engineering principles and how to apply them are imperative to this product development process.

This approach is especially important in novel dosage forms that are used to produce a drug product that may have even tighter tolerances for performance, stability, and/or manufacturability than a standard dosage form. For example, if the release rate of drug is governed by a functional coating, where the coating thickness and morphology impact the rate of release, it becomes critical to control the coating process such that it consistently provides the same coating quality. While this is important for cosmetic coatings too, the range of coating thickness that yields acceptable performance and appearance is much broader than that for a functional coating. This chapter demonstrates the application of energy and mass transport principles to both the dosage form mechanism of release and the manufacturing process for a novel pharmaceutical formulation.

The formulation and process utilized to make a drug product are coupled and each must be examined in the context of the other. For example, in choosing the materials that are used in the formulation it is important to understand the process implications of the selected materials. Similarly, understanding the mechanism of drug release is key to understanding which product attributes are most critical in achieving the target release profile. This knowledge can be used to help guide process design and development.

In this chapter, an osmotic rupturing multiparticulate formulation manufactured by fluid bed coating is used as a model to demonstrate the application of engineering principles to develop a formulation and process for a novel dosage form. The rupturing multiparticulate is designed to provide a burst of drug release at a specific point in time after dosing. The primary use for this type of dosage form would be where a delayed release of drug is required; quite commonly, this is in combination with an immediate release dose of drug in a single unit dose. This approach allows the combination of multiparticulates with different release profiles in a capsule to provide the overall target release for the product.

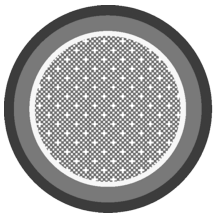
In order to identify a process suitable for manufacture of a formulation, it is important to first understand the critical attributes of the formulation. Second, it is important to have a general understanding of the process, in this case fluid bed coating, to understand the effect of the process equipment

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

and key process parameters on the formulation. Finally, these bodies of knowledge should be combined to design the most appropriate process for manufacture of a specific formulation. This chapter is organized accordingly. We will first introduce the formulation and its mechanism of release in order to understand the critical product attributes. Next, we will discuss the fluid bed coating process from a general perspective. Finally, we will combine knowledge of the formulation and mechanism of release with this general process understanding to discuss specific fluid bed coating process considerations for the rupturing multiparticulate formulation.

35.2 ARCHITECTURE AND FORMULATION

The architecture of the multiparticulate system referred to in this chapter is modeled after formulations described by Ueda et al. [1, 2] and Dashevsky and Mohamad [3]. The release of drug from a rupturing multiparticulate occurs when water passes through a delayed release functional coating into the multiparticulate, builds pressure, and eventually ruptures the delayed release coating, allowing the drug in the multiparticulate to be released. The rupturing multiparticulate is composed of a seed core, surrounded by drug and sweller layers. The final layer is composed of a semipermeable polymer that controls the rate of water ingress. This "delayed release" layer is considered a functional coating since it governs the drug release rate from the multiparticulate. Figure 35.1 illustrates the multiparticulate architecture.



1. Seed core
2. Drug layer
3. Sweller layer
4. Delayed release layer

FIGURE 35.1 Osmotic rupturing multiparticulate architecture.

The various layers of the multiparticulate must have certain attributes in order to achieve the target release profile. In addition, all components that contact the drug must be chemically compatible with it. The general attributes of each component are described below, followed by the specific components used in the model system.

The drug in the model system is adipiplon, a small molecule that has relatively high solubility over a physiologically relevant pH range (>2 mg/mL from pH 1 to 8). For the rupturing multiparticulate formulation, the desired dose was low (<10 mg). The desired release profile was an immediate release dose followed by a pulse of drug 1–3 h after administration. Formulations for delayed release multiparticulates with 1, 2, and 3 h lag times were identified. The osmotic rupturing multiparticulate was selected as the lead approach for pulsatile release. The exact composition of the adipiplon multiparticulate formulation that was developed is shown in Table 35.1. The rationale for choosing the specific components for each layer is presented below.

The seed core material should provide an inert, durable, and smooth substrate for coating. Spherical microcrystalline cellulose (Celphere CP-708) with a mean particle size of 700 μm was used in the model system.

The drug layer should provide immediate drug release once the delayed release coating has ruptured. A water-soluble binder, HPMC E5 premium, was used in the model system with a high drug loading (75% A). The relatively high drug loading was selected to reduce processing time.

The sweller layer should provide sufficient driving force in the form of water activity at a sufficiently rapid rate to hydrate the core up to the point of rupture. The swelling component should be uniformly distributed to provide a smooth coating surface. Milled croscarmellose sodium (Ac-Di-Sol) with a water-soluble binder (HPC, Klucel EF) was used in the model system.

TABLE 35.1 Example Adipiplon Multiparticulate Formulation Composition

Layer	Amount (mg/g Final Multiparticulates)	Component (% in Layer)	Name	Function
Seed core	391.5	700 μm Celphere	Microcrystalline cellulose (Celphere CP-708)	Substrate
Drug layer	14.6	HPMC (25%)	Hypromellose (E5 premium)	Binder
	43.9	API (75%)	API (milled)	Active
Sweller layer	128.6	HPC (28.6%)	HPC (Klucel EF)	Binder
	321.4	Ac-Di-Sol (71.4%)	Croscarmellose sodium (Ac-Di-Sol, milled)	Sweller
Delayed release layer	50	Talc (50%)	Talc (IMP-1889L)	Coating strength modifier
	50	Ethylcellulose (50%)	Ethylcellulose (Ethocel STD 10 cP)	Semipermeable polymer

The delayed release layer has several properties that are critical to the performance of the system. The coating contains a semipermeable polymer that controls water ingress. This makes both the morphology and thickness of the coating critical to the performance. The coating in this layer must also fail via fracture or rupture; ideally the coating is brittle enough that it does not require a large degree of swelling prior to rupture. The semipermeable polymer selected was ethylcellulose. This polymer is commonly used in osmotic systems. A coating strength modifier, talc, was also used to increase the brittleness of the coating. Figure 35.2 shows the effect of two levels of talc on performance. Increasing the level of talc resulted in a much sharper burst, indicating more of the multiparticulates burst in a narrower time window. Figure 35.3 shows the performance of the 1, 2, and 3 h delayed release formulations. All formulations had the same composition differing only in the thickness or coating weight of the delayed release layer. To further understand the mechanism of drug release from this system, a more detailed explanation of the mechanism of release is given in the next section.

35.3 MECHANISM OF RELEASE

The physical model for the mechanism of release from rupturing multiparticulates is shown in Figure 35.4. The target release profile for a rupturing multiparticulate formulation is shown in Figure 35.5. The release profile has two primary components: the lag time, defined as the time between aqueous exposure of the multiparticulates and when rupture of the functional coating is initiated, and the duration of release, defined as the time between when rupturing begins and when drug release from the multiparticulates is substantially complete.

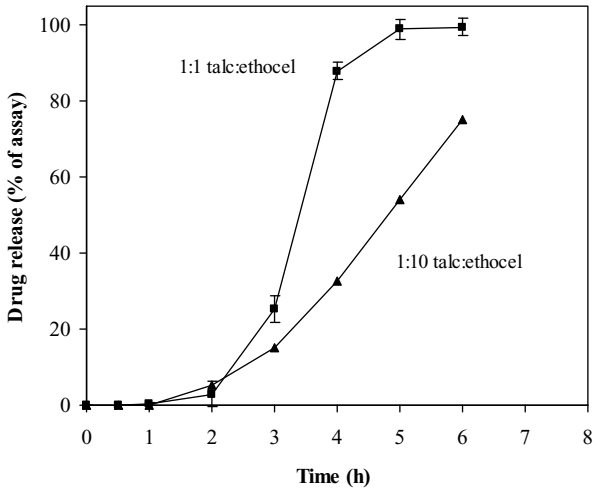


FIGURE 35.2 Effect of talc level in delayed release layer on the performance of adipiplon multiparticulates.

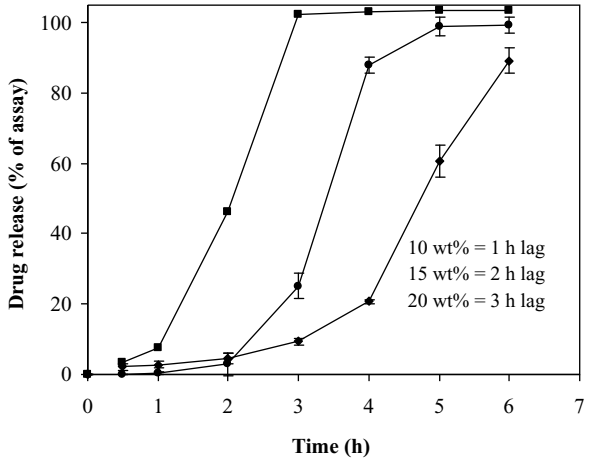


FIGURE 35.3 Effect of delayed release layer coating weight on the performance of adipiplon multiparticulates.

If a dissolution profile on a single multiparticulate were obtained, it would show a lag time dependent on the thickness and composition of the delayed release coating, and would have an immediate release profile once it ruptured (see Figure 35.6). However, since a dosage form consists of hundreds or thousands of multiparticulates, not one single multiparticulate, there is a distribution of final multiparticulate size, with small cores with thin coatings on one end of the distribution and large cores with thick coatings on the other (see Figure 35.7). If this distribution is then translated to predicted performance, multiparticulates with different coating thicknesses would be expected to rupture at different times. If many of these multiparticulates are in a dosage form, then the overall dissolution profile is the composite of many individual dissolution profiles and the overall dissolution profile will have a much broader duration of release (see Figure 35.8). The lag time for the dosage form is then defined as the amount of time prior to the first multiparticulate rupturing and the duration of release is proportional to the breadth of the coating weight distribution.

The mechanism of release from rupturing multiparticulates can be presented mathematically. The water uptake by the multiparticulates can be represented by equation 35.1, as demonstrated for osmotic systems by Theeuwes [4]:

$$\frac{dV_w}{dt} = \frac{A}{h} L_p(\sigma \Delta\Pi - \Delta P) \qquad (35.1)$$

where V_w is the volume of water in the multiparticulate, t is the time, A is the cross-sectional area of the coating, h is the coating thickness, L_p is the mechanical permeability of the coating to water, σ is the reflection coefficient, $\Delta\Pi$ is the osmotic pressure difference across the coating, and ΔP is the hydrostatic pressure difference across the coating.

From a practical formulation approach, using this equation to guide formulation selection ensures the multiparticulate is formulated such that the osmotic pumping term is

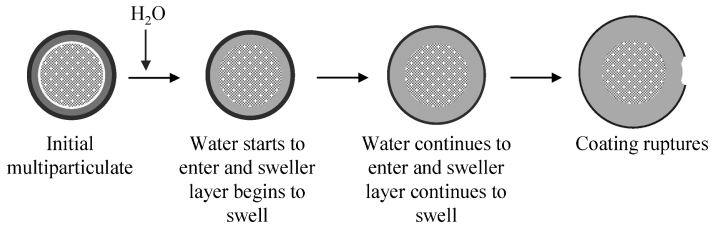


FIGURE 35.4 Mechanism of release for rupturing multiparticulates.

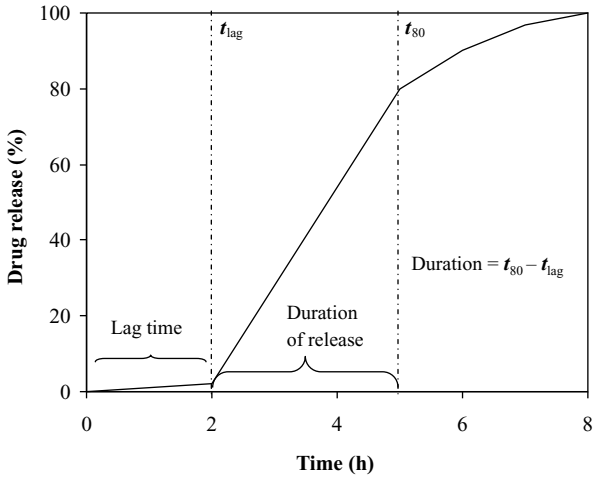


FIGURE 35.5 Example release profile of rupturing multiparticulates.

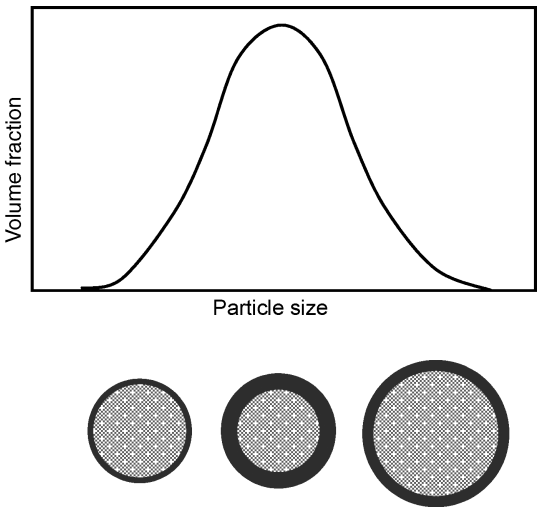


FIGURE 35.7 Coated particle size distribution and bead population.

always significantly greater than the hydrostatic pressure resistance term. This will ensure that the direction of water flow is into the multiparticulates (e.g., $dV_w/dt > 0$) and that the multiparticulates will ultimately rupture.

To examine the hydrostatic pressure difference, ΔP, it is useful to use Laplace's law, as shown in equation 35.2. This law describes the relationship between pressure of a sphere and wall tension or stress.

$$\Delta P = \frac{2E\varepsilon_e h}{r} \tag{35.2}$$

where E is the modulus of elasticity for the semipermeable coating, ε_e is the engineering strain of the system

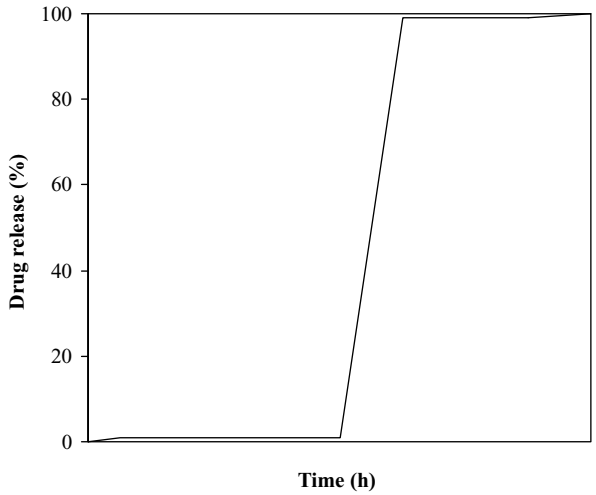


FIGURE 35.6 Single bead dissolution.

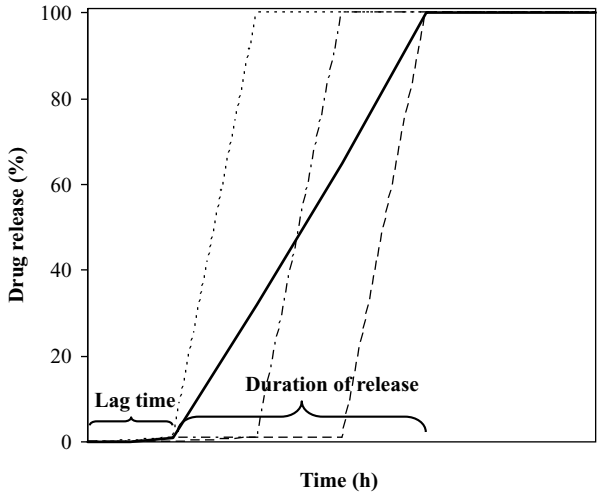


FIGURE 35.8 Composite dissolution profile.

(deformation of the system), and r is the radius of the multiparticulate.

Equation 35.2 assumes that the coating is perfectly elastic and does not yield (i.e., it displays Hookean behavior, where the strain is directly proportional to the stress) while it expands and that the multiparticulates are spherical with the coating thickness significantly smaller than the radius of the multiparticulate. For this system, these are reasonable simplifying assumptions. For $dV_w^*/dt > 0$ (where * denotes the value at rupture), we can combine equations 35.1 and 35.2 to obtain equation 35.3.

$$\sigma\Delta\Pi > \frac{2E\varepsilon_e^* h^*}{r^*} \tag{35.3}$$

Practically, this equation tells us that the pressure required to rupture the coating is directly proportional to the coating's modulus of elasticity E, the engineering strain ε_e (a measure of how much the coating has changed in size), and the thickness of the semipermeable coating. Also, the pressure required to rupture the coating is inversely related to the radius of the multiparticulate; that is, smaller multiparticulates are harder to rupture.

To summarize, from the preceding discussions of the formulation architecture and mechanism of release, critical product attributes include the size and distribution of seed cores, the uniformity of all coating layers, the potency of the drug and sweller layers, and the thickness and morphology of the delayed release layer. Now that the factors governing the release of the drug from the multiparticulates have been discussed, the next section covers understanding the fluid bed coating process both generally and specifically as it pertains to manufacturing this dosage form.

35.4 PROCESS

The primary process used to manufacture the rupturing multiparticulates is Wurster fluid bed coating. In this chapter, when we refer to fluid bed coating it is always Wurster fluid bed coating. To obtain the target performance and have a robust and well-characterized process, it is important to have a good understanding of the fluid bed coating unit operation.

A schematic of a bottom-spray fluid bed coater with Wurster column is shown in Figure 35.9. The fluid bed coater consists of an air distributor plate, a nozzle, a Wurster column, an expansion chamber, and a downbed. Atomizing air and fluidizing air flow from the bottom to the top of the coater.

The fluid bed coating process can be envisioned as controlled circulation of particles through the Wurster column, where coating is applied via coating solution droplets from a two-fluid atomizer. Hot drying gas is introduced at the bottom of the fluid bed where the design of the distributor plate causes the majority of the gas to go up through the Wurster column. As a result, the velocity in the column is much higher than that in the downbed and there is a pressure difference between the column and downbed, causing particles to move from the downbed into the column. These entrained particles are transferred upward through the column where coating is deposited and partially dried. As the particles leave the column, they enter the expansion chamber where the particles continue to dry and the gas velocity drops (due to the equipment geometry) below the minimum entrainment velocity and the particles disengage from the gas stream and fall back to the downbed to start the cycle over again.

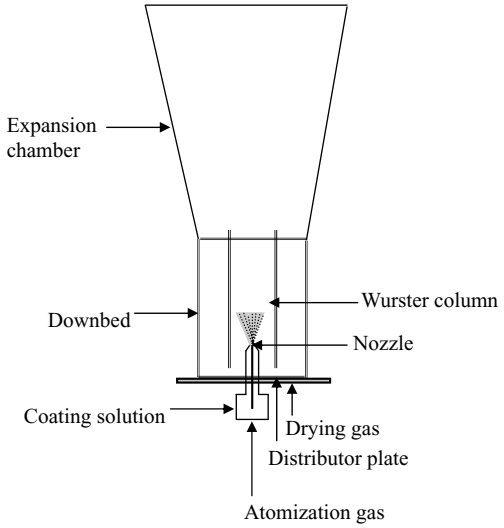


FIGURE 35.9 Fluid bed coater.

There are many subprocesses that occur in a Wurster fluid bed coating process. All of these subprocesses must work appropriately to successfully coat particles. However, in the context of this chapter, the main phenomena that need to be considered in the fluid bed coating process are (1) the frequency of coating and circulation of individual particles as they affect the uniformity of the coating and (2) coating deposition and drying as it directly affects the coating quality. The first phenomenon will be discussed qualitatively in this chapter, while the second phenomenon will be addressed in more detail.

It is important to have a qualitative understanding of the frequency of coating individual particles as it can have a direct impact on the coating uniformity. First of all, it is important to understand that when particles pass through the Wurster column, only a small percentage is actually coated on each pass [5, 6]. The consequence is that in order to uniformly coat all particles, the coating process needs to be long enough to ensure a sufficient number of passes through the spray zone for each particle. In some cases, the coating solution solids content may need to be adjusted to ensure a sufficiently long coating time.

Particle circulation through the fluid bed must also be consistent for all particles in order to achieve uniform coating. Preferential entrainment due to static or particle size, or uneven fluidization of the downbed, can lead to nonuniform coating across particles during the process. Practically, particle circulation can be assessed through visual observations of fluidization, and can be improved through use of a narrower particle size distribution of cores and/or through increasing bed humidity to minimize static accumulation.

As the particles circulate through the Wurster column, coating solution droplets are deposited onto the particles. As the particles continue to circulate through the fluid bed, the coating droplets then dry. The properties of these droplets and the environmental conditions such as temperature and solvent concentration within the fluid bed directly affect the drying rate of both the droplets prior to deposition and the deposited coating. The drying rate can have a significant impact on the coating morphology and therefore the drug release rate if it is a functional coating. At faster drying rates, the coating droplets contain less solvent and produce more porous coatings. These more porous coatings can be both more permeable and mechanically weaker than coatings applied under wetter conditions. Thus, it is important to choose an appropriate drying rate for a particular coating process and ensure that it is maintained throughout the process.

Droplet size can also have a significant effect on the coating properties, since it impacts the drying rate. There are four variables that affect the droplet size: atomization gas flow rate (commonly controlled by pressure), atomizer design, spray rate, and solution properties. From a practical standpoint, the last three variables are usually fixed for a given process and equipment train, leaving the atomization gas flow rate as the most common process variable. For most solutions, once there is sufficient atomizing gas flow to fully atomize the solution, there is generally a small effect of atomizing gas on droplet size (see Figure 35.10) [7].

The three process parameters that affect the droplet drying/coating formation conditions are drying gas flow rate, drying gas temperature, and spray rate. Practically, drying gas flow rate is constrained as it is coupled to particle circulation, leaving spray rate and inlet temperature as variables. It is often helpful to evaluate the effect of these parameters on the driving forces for heat and mass transfer, namely, the dependent variables of bed temperature and solvent concentration. Figure 35.11 shows such a plot for an aqueous coating system with constant bed temperature and humidity lines. Such a plot can be constructed for any solvent/drying gas coating system using mass and energy balances and is demonstrated later in this chapter.

In the upper left-hand corner of the plot, there is a low driving force for mass transfer and thus slower drying rates. Moving to the lower right-hand corner, the solvent concentration decreases and temperature increases, resulting in much faster drying rates and thus decreasing coating efficiency and increasing coating porosity.

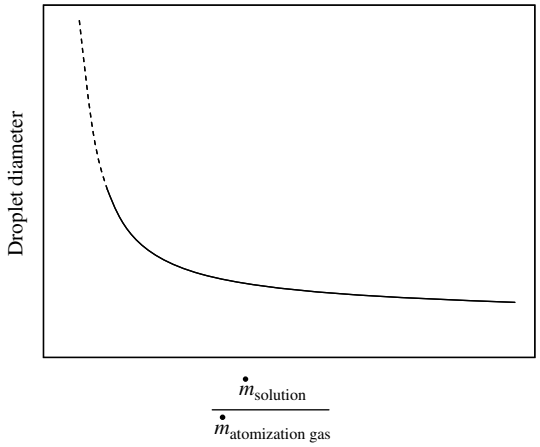


FIGURE 35.10 Droplet size as a function of $\dot{m}_{\text{solution}}/\dot{m}_{\text{atomization gas}}$.

This plot can be overlaid with the practical limitations of the coating process (some of which are determined experimentally) as shown in Figure 35.12 to define the acceptable processing space. This process map can be used as a guide to understand the effect of process variables on product properties within the process space.

35.4.1 Mass and Energy Balance

To understand the overall process on a macroscopic scale and draw the process plots, it is necessary to evaluate the overall mass and energy balance for the unit operation. The objective is to evaluate the overall system when operating at steady state with a control volume drawn around the entire system, as shown in Figure 35.13. Using the principles of the

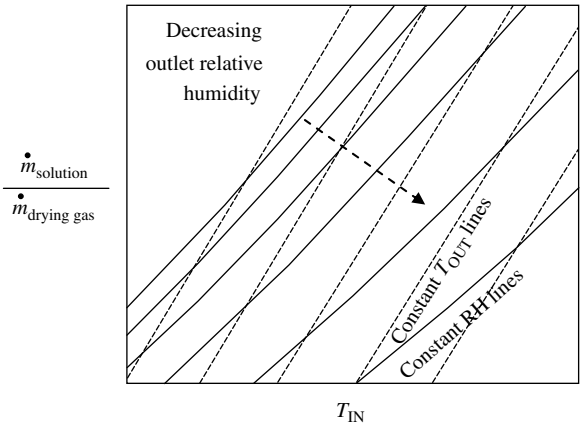


FIGURE 35.11 Outlet temperature and relative humidity as a function of $\dot{m}_{\text{solution}}/\dot{m}_{\text{drying gas}}$ versus T_{IN}.

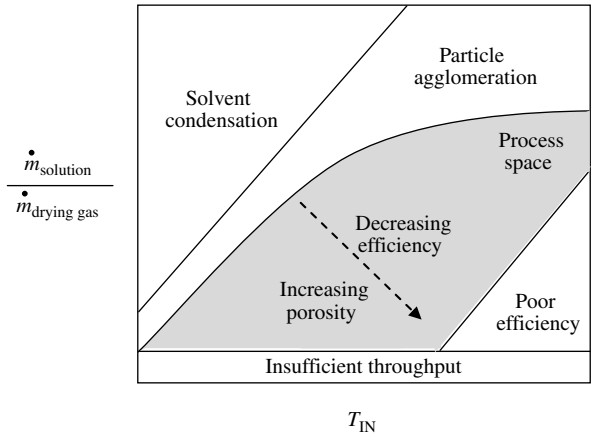


FIGURE 35.12 Conceptual process space.

conservation of mass and the first law of thermodynamics, the inputs of this control volume must be equal to the outputs plus any accumulation that occurs in the control volume.

The inputs into the control volume are

- mass flow rate, temperature, and solids content of the coating solution,
- mass flow rate, inlet temperature, and relative humidity of the drying gas, and
- mass flow rate, temperature, and relative humidity of the atomization gas.

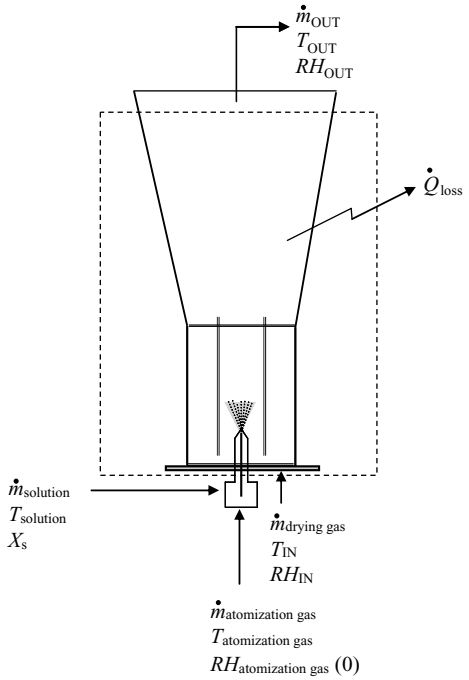


FIGURE 35.13 Control volume for fluid bed coater.

The outputs from the process are

- mass flow rate, outlet temperature, and relative humidity of the exiting gas stream, and
- the heat loss from the system.

If an energy balance on the system at steady state is done and it is assumed that potential and kinetic energy changes are negligible, the following equation can be written:

$$\dot{m}\,\Delta H = \dot{Q} + \dot{W} \tag{35.4}$$

where $\dot{m}\,\Delta H$ is the change in enthalpy for the system, $\dot{Q}$ is the rate of heat flow into the system, and $\dot{W}$ is the rate of work done on the system.

It is assumed that there is negligible work done on the system and that the enthalpy contributions of the spray solids and atomizing gas are negligible. Therefore, only the enthalpy contributions of the drying gas and the solution are significant. Furthermore, it is assumed that the heat of vaporization is constant with respect to temperature and the spray solvent is completely evaporated. Under these conditions, the energy balance can be written as follows:

$$\dot{m}_{dgas} C_{p\ dgas} \Delta T_{dgas} + \dot{m}_{solution}(1-x_S) C_{p\ solution} \Delta T_{solution} + \dot{m}_{solution}(1-x_S)\lambda_v = \dot{Q} \tag{35.5}$$

where $\dot{m}$ is a mass flow rate, C_p is specific heat, x_S is the solid fraction in the coating solution, and λ_v is the enthalpy of vaporization.

This equation can be rearranged to solve for the drying gas outlet temperature to construct the lines in Figure 35.11. Similarly, the lines of constant humidity (or solvent) can be constructed using psychometric principles [8].

Now that the formulation, the mechanism of release, and the general fluid bed coating process have been discussed, we can use this information to understand critical process parameters for manufacture of rupturing multiparticulates.

35.4.2 Process Considerations Specific to Rupturing Multiparticulates

As was discussed in Section 35.3, critical product attributes for rupturing multiparticulates are particle size and distribution of the seed core, uniformity of the coating for all layers, and the coating morphology and thickness for the delayed release layer. Specific processing considerations for rupturing multiparticulates that impact the critical product attributes are discussed below.

35.4.2.1 Seed Core Many types of particles with a wide range of sizes can be coated in a fluid bed coater. In general, with smaller particles, minimizing static, ensuring uniform coating thickness particle to particle, and running the process with high efficiency is more challenging than for large

particles. Large particles present their own set of process challenges such as maintaining good fluidization while minimizing attrition.

The key properties of the seed core that are important to achieving a uniform coating for all layers are the particle size and size distribution. The seed core size and distribution serves as the basis for the overall final multiparticulate size and distribution. As discussed in Section 35.3, this is important because the thickness of the coating on each particle affects when that multiparticulate bursts.

Based on this understanding, it is very important in cases where a sharp delayed release pulse is desired to start the process with as narrow a particle size distribution of seed cores as possible. Furthermore, it is critical to run the process to minimize the breadth of the size distribution for the final coated multiparticulates. In some cases, sieving the starting seed cores to narrow the distribution may be appropriate.

35.4.2.2 Uniformity of Coatings: Drug Layer and Sweller Layer The critical product attributes for the drug and sweller layer are uniformity of the coating and achieving target potency of either drug or sweller. To ensure uniformity of the coating, good atomization, sufficiently long process time, and good particle circulation are required during the process. To ensure that the potency of the drug and sweller is as desired, the coating efficiency should be high (i.e., efficiency as a function of process conditions should be understood and maximized).

Particle size can be a factor for materials applied as suspensions. A rule of thumb for coating multiparticulates is that particles in suspension should be at least one order of magnitude smaller in their longest dimension than the size of the core being coated. This aids in obtaining high coating efficiency.

35.4.2.3 Delayed Release Layer In addition to uniformity of the coating being critical for the delayed release layer, as we have seen in our discussion of mechanism of release, the morphology of this coating (e.g., porosity) is also critical to performance. As discussed, the drying rate of droplets has significant impact on coating porosity. Based on this, the acceptable process space for coating this layer is further constrained not only by efficiency but also by product performance. Practically, once the process map introduced in Section 35.4 is established for this process, it can be used to define a range of processing parameters that result in acceptable product performance.

35.5 SUMMARY

The key to developing a successful novel dosage form from a processing perspective is understanding the underlying mechanism of release of the dosage form, the unit operations used in the process, and how the key process variables impact the product properties. While this can be more complex with novel dosage forms, the principles remain the same for all dosage form development.

35.6 PROBLEMS

1. An ethylcellulose-based delay release coating, having an elastic modulus of 500 MPa and elongation at failure of 3%, is applied to a formulated core that is 1 mm in diameter. The coating is applied to achieve 25 wt% coating weight. Assuming the coating and formulated core have similar densities, and the final dosage form has a displaceable volume of 0.2 mm^3,
   (a) What is the hydrostatic pressure required to rupture the coating?
   (b) What is the volume of water required to rupture the coating?
2. Given the information from the previous problem, and assuming a mechanical permeability of the membrane of 5×10^{-7} $cm^2/(atm\,h)$, a reflection coefficient of 1, and a constant osmotic pressure difference of 50 atm between the media and the core, what is the approximate time to hydrate the core?
3. An aqueous suspension of ethylcellulose, TEC, and talc at 20 wt% total solids is being coated onto formulated multiparticulates in a fluid bed coater. The drying gas is conditioned to an inlet temperature of 55°C and a measured dew point of 10°C. The air flow rate is 600 cfm and the solution spray rate is 15 kg/h. Assuming all the solvent is evaporated, the solution is at 20°C, and the rate of heat loss is approximately 20 kJ/min,
   (a) Estimate the temperature of the bed.
   (b) What is the relative humidity of the exhaust gas?

35.7 PROBLEM SOLUTIONS

1. (a) Based on the applied coating, first the coating thickness and the starting particle radius must be determined. Assume that $h \ll r$ and the coating and core are of similar density.

$$h = \frac{1}{3}\frac{\rho_{\text{bead}}}{\rho_{\text{coat}}}\left(\frac{X_{\text{coat}}}{1-X_{\text{coat}}}\right)r$$

$$h_0 = \frac{1}{3}(1)\left(\frac{0.25}{1-0.25}\right)\left(\frac{1.00\,\text{mm}}{2}\right) = 0.056\,\text{mm} = 56\,\mu\text{m}$$

$$r_0 = \left(\frac{1.00\,\text{mm}}{2} + 0.056\,\text{mm}\right) = 0.556\,\text{mm} = 0.56\,\text{mm}$$

Plug these values into the equation for the hydrostatic pressure difference term at the point of failure indicated below:

$$\Delta P^* = 2E\frac{h_0}{r_0}\frac{\varepsilon_e^*}{\left(1+\varepsilon_e^*\right)^3}$$

$$\Delta P^* = 2(500\,\text{MPa})\left(\frac{0.056\,\text{mm}}{0.556\,\text{mm}}\right)\left(\frac{0.03}{(1.03)^3}\right)$$

$$= 2.8\,\text{MPa} = 27\,\text{atm}$$

(b) The amount of water is equal to the displaceable volume plus the change in volume of the expanding particle (based on its strain). Use the definition of strain to define what the volume of the particle will be at the point of coating failure indicated below:

$$V_{\text{bead}}^* = V_0\left(1+\varepsilon_e^*\right)^3$$

$$V_w^* = V_d + V_0\left[\left(1+\varepsilon_e^*\right)^3 - 1\right]$$

$$V_w^* = 0.2\,\text{mm}^3 + \frac{4\pi}{3}(0.556\,\text{mm})^3(1.03^3-1) = 0.27\,\text{mm}^3$$

3. (a) Based on the defined inputs of inlet temperature and dew point for the drying gas, a psychrometric chart [9] can be used to define the properties of the drying gas, namely, the specific volume and humidity, determined to be 0.94 m^3/kg dry air (DA) and 0.0076 kg/kg DA, respectively. The heat capacity of water was taken to be 4.186 kJ/(kg °C), and enthalpy of vaporization 2390 kJ/kg (for 310 K). The specific heat for the moist air was interpolated to be 1.026 kJ/(kg °C) based on the individual values for air and water.

First determine the mass flow rates of both dry and moist air.

$$\dot{m}_{DA} = (600\,\text{ft}^3/\text{min})(\text{m}^3/35.315\,\text{ft}^3)(\text{kgDA}/0.94\,\text{m}^3)$$

$$= 18.07\,\text{kg/min}$$

$$\dot{m}_{\text{dgas}} = 18.07\,\text{kg/min} + 18.07\text{kg DA/min}(0.0076\,\text{kg/kg DA})$$

$$= 18.21\,\text{kg/min}$$

Rearrange equation 35.5, and solve for the outlet temperature using units on a per minute basis (i.e., 15 kg/h is 0.25 kg/min).

$$T_{\text{OUT}} = \frac{\dot{m}_{\text{dgas}}C_{p\ \text{dgas}}T_{\text{IN}} + \dot{m}_{\text{solution}}(1-x_S)C_{p\ \text{solution}}T_{\text{solution}} + \dot{Q} - \dot{m}_{\text{solution}}(1-x_S)\lambda_v}{\dot{m}_{\text{dgas}}C_{p\ \text{dgas}} + \dot{m}_{\text{solution}}(1-x_S)C_{p\ \text{solution}}}$$

$$T_{\text{OUT}} = \frac{18.21(1.026)(55) + 0.25(1-0.20)(4.186)(20) + (-20) - 0.25(1-0.20)(2390)}{18.21(1.026) + 0.25(1-0.20)(4.186)} = 28^\circ\text{C}$$

2. Use the differential equation for the volumetric flow rate of water through the semipermeable membrane (equation 35.1). By assuming that the coating thickness and surface area do not change during the time of hydrating the core, the equation can be simplified since the hydrostatic pressure difference is negligible, and integrated to result in the following relationship:

$$\int_0^{V_d} dV_w = \frac{4\pi r_0^2}{h_0}L_p\sigma\Delta\Pi \cdot \int_0^t dt$$

Solving for time,

$$t_{\text{hydrate}} = \frac{V_d h_0}{4\pi r_0^2 L_p \sigma \Delta\Pi}$$

$$t_{\text{hydrate}} = \frac{2\times10^{-4}\,\text{cm}^3(0.0056\,\text{cm})}{4\pi(0.0556\,\text{cm})^2(5\times10^{-7}\,\text{cm}^2/(\text{atm h}))(1)(50\,\text{atm})} = 1.2\,\text{h}$$

(b) Evaluate the mass balance for water in the system and solve for the outlet humidity assuming complete evaporation of solvent.

$$H_{\text{OUT}} = H_{\text{IN}} + \frac{\dot{m}_{\text{solution}}(1-x_S)}{\dot{m}_{\text{DA}}}$$

$$H_{\text{OUT}} = 0.0076 + \frac{0.25(1-0.20)}{18.07} = 0.0187\,\text{kg/kg DA}$$

The psychometric chart can be used to interpolate the relative humidity of the exhaust gas at the calculated outlet temperature of 28°C, or alternatively the humidity can be converted into a partial pressure of water vapor, and Antoine's equation used to calculate the saturation pressure for the solvent at the calculated outlet temperature.

$$\text{RH}_{\text{OUT}} = 78\%$$

ACKNOWLEDGMENT

The authors wish to acknowledge Neurogen Corporation for allowing us to use adipiplon osmotic rupturing multiparticulate data in the presentation of the material in this chapter.

REFERENCES

1. Ueda, S., et al. *J. Drug Target.*, 1994;2:35–44.
2. Ueda, S., et al. *Chem. Pharm. Bull.* 1994;42(2):359–363.
3. Dashevsky, A., Mohamad, A. *Int. J. Pharm.* 2006;318:124–131.
4. Theeuwes, F. *J. Pharm. Sci.* 1975;64(12):1987–1991.
5. Cheng, X. X. Turton, R., *Pharm. Dev. Technol.*, 2000;5(3): 311–322.
6. Cheng, X. X. Turton, R., *Pharm. Dev. Technol.*, 2000;5(3): 323–332.
7. Masters K. *Spray Drying Handbook*, 4th edition, Wiley, New York, 1985, pp. 236–252.
8. McCabe W, Smith J, Harriott P. *Unit Operations of Chemical Engineering*, 6th edition, McGraw-Hill, New York, 2001, pp. 596–621.
9. Moyers C, Baldwin G. Psychrometry, evaporative cooling, and solids drying. In: Perry R, Green D, Maloney J, editors, *Perry's Chemical Engineers' Handbook*, 7th edition, McGraw-Hill, New York, 1997.