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Research Article

Using a Mass Balance to Determine the Potency Loss during the Production of a Pharmaceutical Blend

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Abstract. The manufacture of a blend containing the active pharmaceutical ingredient (API) and inert excipients is a precursor for the production of most pharmaceutical capsules and tablets. However, if there is a net water gain or preferential loss of API during production, the potency of the final drug product may be less than the target value. We use a mass balance to predict the mean potency loss during the production of a blend via wet granulation and fluidized bed drying. The result is an explicit analytical equation for the change in blend potency a function of net water gain, solids losses (both regular and high-potency), and the fraction of excipients added extragranularly. This model predicts that each 1% gain in moisture content (as determined by a loss on drying test) will decrease the API concentration of the final blend at least 1% LC. The effect of pre-blend solid losses increases with their degree of superpotency. This work supports Quality by Design by providing a rational method to set the process design space to minimize blend potency losses. When an overage is necessary, the model can help justify it by providing a quantitative, first-principles understanding of the sources of potency loss. The analysis is applicable to other manufacturing processes where the primary sources of potency loss are net water gain and/or mass losses.

KEY WORDS: drug product manufacture; mass balance; overage; QbD; wet granulation.

INTRODUCTION

A common unit operation in the manufacture of pharmaceutical solid oral dosage forms is the production of an "active" powder/granule blend. Chemically, the active blend consists of a mixture of the active pharmaceutical ingredient (API) and one or more excipients. The excipients are biologically inert, but may serve as drug diluents, improve the powder flow, control release of the API *in vivo*, etc. Depending on the final dosage form, this blend may be compressed into tablets, filled into capsules, or, in the case of a "sprinkle" formulation, not processed further. In all cases, the assay of the intermediate active blend affects the assay of the final dosage form.

Several methods may be used to produce the active blend. The simplest method, direct blending, involves directly blending the API and excipients, followed immediately by tablet compaction or capsule filling. However, this method often cannot be used because the resultant powder mix does not have sufficient flowability and/or compressibility to be robustly processed into capsules or tablets. Most other processing methods involve powder agglomeration to improve the flowability and/or compressibility of the final powder blend. Most powder agglomeration processes (*e.g.*,

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ABBREVIATIONS: a, API; e, Excipients; f, Final; w, Water; B, Blend; G, Granulation; R, Regular potency; SP, Subpotent or superpotent; 0, Initial; API, Active pharmaceutical ingredient; LC, Label claim potency; LOD, water content of solids (% *w*/*w*)

NOMENCLATURE: $m_{B,a;0}$, mass of API added during blending (kg); $m_{B,a;f}$, mass of API in final blend (kg); $m_{B,e;0}$, mass of excipients added during blending (kg); $m_{B;f}$, final mass of blend (kg); $m_{B;o}$, $\equiv m_{G;0} + m_{B,a;0} + m_{B,e;0}$, total theoretical mass of solids entering blender (kg); $m_{G,a;f}$, mass of API in the final dried, milled granules (kg); $m_{G,a;0}$, mass of API added to granulation (kg); $m_{G,0}$, total mass of API and excipients added to granulator (kg); $m_{G;f}$, final mass of dried, milled granules (kg); m_W, mass of water in sample (kg); m_S, mass of solids in sample, normalized to incoming water content (kg); m_T, total mass of sample, m_W+m_S (kg); $x_{B,a}$, final mass fraction of API in final blend (−); $x_{B,a;0}$, mass fraction of API in all added granulation and blend solids (−); x_{Bxtra}, mass fraction of solids that are added extragranularly (−); $x_{G,a}$, mass fraction of API in the final dried, milled granules (−); $x_{G,a;0}$, mass fraction of API in the added granulation ingredients (−); $L_{G,R}$, $\equiv \Delta m_{G,R}/m_{G;0}$, fraction of regular potency solids lost during granule processing (−); $L_{G,SP}$, $\equiv \Delta m_{G,SP}/m_{G;0}$, fraction of sub/superpotent solids lost during granule processing (−); $P_{B;f}$, final mean blend potency (% of theoretical); $P_{G,f}$, mean potency of the dried, milled granules (% of theoretical); $P_{G,SP}$, mean potency of sub/superpotent mass losses during granule processing (% of theoretical); Δm_w, net water gain during granule processing (kg); Δm_G, total mass loss during granule processing (kg); $\Delta m_{G,a}$, mass loss of API during granule processing (kg); $\Delta m_{G,R}$, mass of regular potency solids lost during granule processing (kg); $\Delta m_{G,SP}$, mass of super or subpotent solids lost during granule processing (kg); ΔLOD, change in water content of solids (% *w*/*w*); $\Delta P_{B;f}$, mean reduction of final blend potency from theoretical (% of theoretical).

low and high-shear granulation with a liquid binder (1,2), fluidized bed granulation (3, extrusion and spheronization (4), etc.), with the exception of dry granulation (roller compaction (5)) usually involve the addition of water in an early step and therefore the removal of the water, often via an evaporative drying unit operation, in a later step (6). The "drying endpoint", defined as the acceptable range of water content for material exiting the dryer, is generally chosen to yield acceptable processability (*e.g.*, tablet compactibility) (6) of the granules and/or stability of the final drug product (7). The drying endpoint is generally not considered a potential quality attribute for drug product assay (8). However, if the processing yields a net water gain or loss, relative to the incoming solids, the assay of the dried granules (API per unit mass) may be higher or lower than the theoretical value due to the unaccounted for mass change due to water. If the mean net water gain averaged over many processing batches is not close to zero, the mean drug product potency may show a systematic deviation from the target value. A challenging issue may arise if the final granules "need" to contain more or less water than the incoming dry powders, to have the desired flow and/or tablet-forming properties. In this case, a change in granule mass potency relative to the incoming solids ingredients will be an endemic part of the process.

Another potential cause of blend potency reduction is fluidized bed drying (6), which is commonly used to dry the wet pharmaceutical intermediates. This unit operation involves blowing heated air through a wet powder bed. Often, the API particle size is smaller than that of the other excipients. Smaller particles are more likely to be entrained in the upward airflow longer (9), adhering to the filters at the top of the dryer, hence comprising a larger fraction of the material lost through the filter bags.

In situations where the drug product manufacturing process consistently results in a reduction in potency, an API overage may be added to compensate for the process losses. The US Food and Drug Administration's most recent guidance addressing this, ICH Q8 Pharmaceutical Development (10), still allows the addition of an overage. However, this guidance, as well as the more recent draft update (11), outlines the importance of understanding the process "design space", defined as the range of process parameters the yield product with acceptable critical product quality attributes, such as acceptable potency. This suggests the increasing importance of understanding the relationship between measurable process attributes and blend potency changes.

The purpose of this investigation is to use a mass balance to quantify the sources of potency loss during the production of a powder blend via wet granulation and fluidized bed drying. This process is chosen because it requires a relatively large number of process steps; most other blend production processes can—at least considering the mass balance—be considered to consist of a subset of the wet granulation processing steps. Each unit operation is characterized by the mass flow of materials entering and exiting the operation, both intended and unintended. For mass losses that may be subpotent or superpotent, a potency deviation factor is added to the equations. The result is an equation relating measurable process quantities (net water gain, mass loss of "normal potency" solids, and mass loss of "high/low potency" solids) to the potency of the final blend. Since this equation has several independent variables, graphs are presented to facilitate its interpretation. This work can aid QbD by providing a quantitative physical understanding of the sources of potency loss. This can serve two purposes. First, in situations where the design space to yield an active blend with acceptable processability (*e.g.*, flowability or compactibility) overlaps with the design space for acceptable blend potency, it can be used to determine how to eliminated potency losses through the rational selection of in-process limits. For example, if acceptable tablet compressibility is achieved at a blend loss on drying test (LOD) range of 1.0–5.0% *w*/*w*, but LOD values >3.0% *w*/*w* yield unacceptably low blend potency, in-process LOD specification may be set at 1.0–3.0% *w*/*w*. Secondly, there may be situations where the design space to yield an active blend with acceptable processability (*e.g.*, flowability or compactibility) does not overlap with the design space for acceptable blend potency. In this case, although an API overage will be necessary, the model facilitates a quantitative understanding of the sources of potency reduction, and hence a stronger justification for the overage.

THEORY

We consider the production of an "active" powder/granule using the following process train: wet granulation→deagglomeration/delumping (passing the wet granules through a coarse mill screen to break up large "lumps")→fluidized bed drying→sifting/milling→blending. Table I shows the mass balance for each unit operation. The mass losses are subdivided into intended losses (*i.e.*, water during fluidized bed drying), unintended losses having the "correct potency" (representative of the total solids in the process, *e.g.*, wet granules that remain in the mixing bowl), and unintended losses that are "subpotent" or "superpotent" (*e.g.*, API-enriched powders entrained in the fluidized bed dryer exhaust air). For the purposes of analyzing the mass balance to determine potency changes in the solids, we divide this set of process steps into two groups: (1) Wet Granulation→Milling and (2) Blending. Milling is chosen because manufacturing batch records are often written with wet granulation, deagglomeration, drying, and sifting/milling together in a single section, with material weight only being measured after sieving/milling. It is also a reliable step to measure the potency of the solids, since the added water has been removed, and the milled granules are relatively homogeneous.

Mass Balance: Wet Granulation through Milling

Figure 1 shows the total mass balance for wet granulation, deagglomeration, drying, and sifting/milling. API, excipients, and water enter the process and dried granules exit. The only intended process loss is the removal of the granulation water during drying. Representative process losses occur during the transfer between unit operations, *e.g.*, wet mass that remains adhered to the granulation mixing blade or the deagglomeration mill. Superpotent solids losses may occur when material is fluidized, since API particles are often smaller than the excipients and hence more likely to be entrained in an exiting airflow. This is most likely to occur during fluidized bed drying, due to the nature of the unit

Table I. Mass Balance for Each Unit Operation

	Unit Operation(s)				
	Wet granulation	Deagglomeration	Fluidized bed drying	Sifting/milling	Blending
Entering process	Excipients API Water	Wet granules, agglomerated	Wet granules, deagglomerated	Dried granules, unmilled	Extragranular excipients Dried granules, milled
Intended losses	NONE	NONE	Water (entrained in air)	NONE	NONE
Unintended losses: Super or subpotent	Non-representative powder loss during dry mix	NONE	Non-representative solids entrained in dryer exit air	Non-representative solids losses during sifting/milling	Non-representative solids losses during processing (*i.e.* – absorption of low drug load API onto blender surface)
Unintended losses: Correct potency	Representative powder loss during dry mix Wet granules lost post-processing	Wet granules lost post-processing	Representative solids entrained in dryer exit air Dried granules lost post-processing	Representative solids losses during sifting/milling Milled granules lost post-processing	Blend lost post-processing

operation. For a low-potency blend, API could also be removed from the blend by adsorbance onto internal equipment surfaces. However, we will not consider the latter case for our analysis.

The second source of mass change is net water gain or loss. The former will occur if not all the added water is entirely removed during drying. The latter will occur if the drying removes not only the water added during granulation, but also some of the water present in the incoming API and/or excipients. Note that, even if the drying process yields consistent dried granule water content, variation in the water content of the incoming materials could result in batch-to-batch variation in the net water gain/loss. Also note that for the subsequent analysis, all solid masses are based on weight normalization to the water content of the initial dry mix (see Appendix for details).

We develop mathematical expressions for the mass balances for each unit operation (or lumped group of operations) for the total mass, API mass, and water mass. Since there is no creation or destruction of mass, the total mass entering and leaving each unit operation must be the same. If we assume there is no chemical reaction involving API and/or water, the same applies for both of these materials (12). Note that, even if the API and water react to form a hydrate or increase the hydration number of the API,

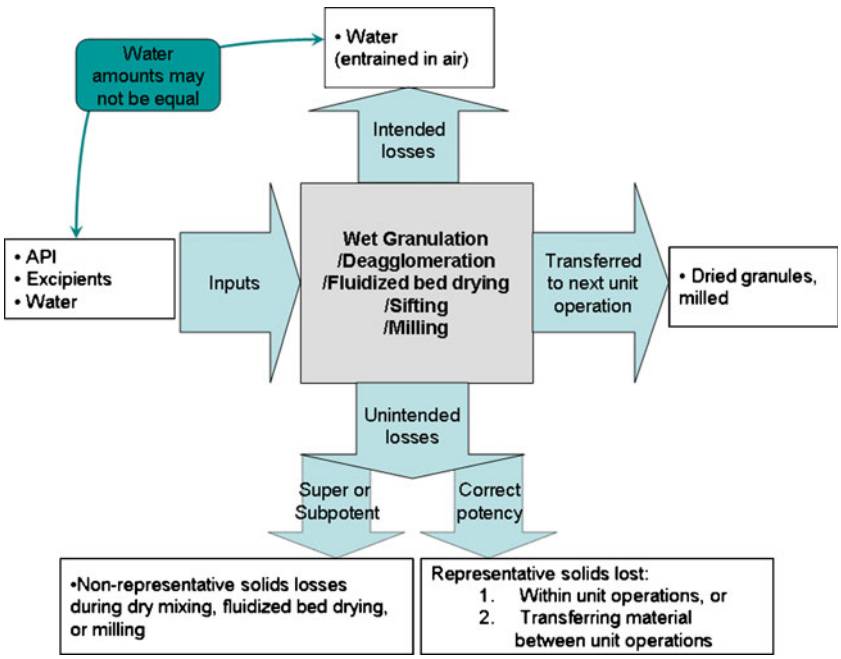

Fig. 1. Total mass balance for production of milled granules by wet granulation, deagglomeration, drying, and sifting/milling

the subsequent analysis will still apply if the increase in hydration water can be quantified—such as by an appropriate choice of LOD temperature/time or other methods. This is because the effect of net water gain on diluting the potency of the blend, defined as the free acid, free base, or neutral compound per unit mass, is the same rather if the net added water is bound via hydration to the API or not.

The mean potency of the final dried and milled granules, $P_{G,f}$, is defined as the ratio of the actual mass fraction of API in the final granules, $x_{G,a}$, to that in the added ingredients, $x_{G,a;0}$:

$$P_{G,f} \equiv \frac{x_{G,a}}{x_{G,a;0}} = \left(\frac{m_{G,a;f}}{m_{G;f} + \Delta m_W}\right) / \left(\frac{m_{G,a;0}}{m_{G;0}}\right) \quad (1)$$

where Δm_W is the increase in the mass of water in the solids during the production of the granules. The final mass of API in the final granules, $m_{G,a;f}$, is the initial mass of API added to the granulator, $m_{G,a;0}$, minus any processing losses of API, $\Delta m_{G,a}$.

$$m_{G,a;f} = m_{G,a;0} - \Delta m_{G,a} \quad (2)$$

The final total mass of the granules, $m_{G;f}$, is the initial total mass of solids added to the granulator (API and excipients), $m_{G;0}$, minus the total solids mass losses, Δm_G

$$m_{G;f} = m_{G;0} - \Delta m_G \quad (3)$$

Substituting Eqs. 2 and 3 into Eq. 1 yields:

$$P_{G;f} = \left(\frac{m_{G,a;0} - \Delta m_{G,a}}{m_{G;0} - \Delta m_G + \Delta m_W}\right) / \left(\frac{m_{G,a;0}}{m_{G;0}}\right) \quad (4)$$

The total solid mass losses consists of both solids that have the same ratio of API to excipients as the incoming material, $\Delta m_{G,R}$, and those that are either subpotent or superpotent, $\Delta m_{G,SP}$:

$$\Delta m_G = \Delta m_{G,R} + \Delta m_{G,SP} \quad (5)$$

We can also write an expression for the mass loss of API as a function of $\Delta m_{G,R}$ and $\Delta m_{G,SP}$:

$$\Delta m_{G;a} = \left(x_{G,a;0} \times \Delta m_{G,R}\right) + \left(x_{G,a;0} \times P_{G,SP} \times \Delta m_{G,SP}\right) \quad (6)$$

where $P_{G,SP}$ is the fraction of API in any subpotent or superpotent solid losses, relative to that in the incoming material. This will be >100% for losses that are "superpotent" and <100% for losses that are subpotent.

Using the results of the analysis in the Appendix, the change in the mass of water, Δm_W, is

$$\Delta m_W \cong \Delta\text{LOD} \times m_{G;f} = \Delta\text{LOD} \times (m_{G;0} - \Delta m_G) \quad (7)$$

Where ΔLOD is the change in the "loss on drying" between the solids entering the granulator and the dried, milled granules.

Substitution of Eqs. 5–7 into Eq. 4 yields

$$P_{G;f} = \left(\frac{m_{G,a;0} - x_{G,a;0} \times \left(\Delta m_{G,R} + \left(P_{G,SP} \times \Delta m_{G,SP}\right)\right)}{\left(m_{G;0} - \Delta m_{G,R} - \Delta m_{G,SP}\right) \times (1 + \Delta\text{LOD})}\right) \Big/ \left(\frac{m_{G,a;0}}{m_{G;0}}\right) \quad (8)$$

Substituting in the definition of $x_{G,a;0}$ and dividing through by the denominator yields

$$P_{G;f} = \frac{1 - \frac{\left(\Delta m_{G,R} + \left(P_{G,SP} \times \Delta m_{G,SP}\right)\right)}{m_{G;0}}}{\left(1 - \frac{\Delta m_{G,R}}{m_{G;0}} - \frac{\Delta m_{G,SP}}{m_{G;0}}\right) \times (1 + \Delta\text{LOD})} \quad (9)$$

To simplify the notation, we define $L_{G,R} \equiv \Delta m_{G,R}/m_{G;0}$ and $L_{G,SP} \equiv \Delta m_{G,SP}/m_{G;0}$ as the mass percent of regular and sub/superpotent solids lost during granule processing. Taking advantage of that $L_{G,R}$, $L_{G,SP}$, and ΔLOD are all typically <<1, and utilizing the Taylor series expansion $1/(1-x) \cong 1 + x$ for x<<1. Equation 9 can be rewritten as:

$$P_{G;f} \cong \left[1 - L_{G,R} - \left(P_{G,SP} \times L_{G,SP}\right)\right] \times \left[1 + L_{G,R} + L_{G,SP} - \Delta\text{LOD}\right] \quad (10)$$

Expanding the terms and taking advantage of the fact that all of the terms involving variables are <<1 yields

$$P_{G;f} \cong 1 - L_{G,SP} \times \left(P_{G,SP} - 1\right) - \Delta\text{LOD} \quad (11)$$

From Eq. 11, we see that the mean potency reduction of the dried granulation is proportional to the product of the mass loss of superpotent solids and the their degree of "superpotency", $P_{G,SP}$ −1. The potency reduction is also a linear function of both net water gain, ΔLOD. The "regular potency" solids losses, $L_{G,R}$, do not affect the final granule potency.

Mass Balance: Blending

Blending involves the mixing of "extragranular" excipients with the dried granules. For the subsequent analysis, we assume:

1. All of the active in the blend comes from the granules (no API is in the extragranular material, $m_{B,a;0}$=0), so $m_{B,a;f}$=$m_{G,a;f}$
2. There are no significant mass losses during blending. Note that, if we relaxed this assumption and simply assume that any material losses during blending are at the same potency as the material entering the blender, the analysis would yield the same potency.
3. There is no net water gain or loss during blending.

Similar to Eq. 1 for the granulation, the potency of the final blend can be defined as

$$P_{B,f} \equiv \frac{x_{B,a}}{x_{B,a;0}} = \left(\frac{m_{G,a;f}}{m_{B;f} + \Delta m_W}\right) / \left(\frac{m_{G,a;0}}{m_{B;0}}\right) \quad (12)$$

An expression for $m_{G,a;f}$ can be obtained by rearranging Eq. 1:

$$m_{G,a;f} = P_{G,f} \times \frac{m_{G,a;0}}{m_{G;0}} \times \left(m_{G;f} + \Delta m_W\right) \quad (13)$$

Next, the final mass of solids in the blend $m_{B;f}$ can be written as the sum of the final granulation solids and the entering blend excipients:

$$m_{B;f} = m_{G;f} + m_{B,e;0} \quad (14)$$

Similarly, the theoretical mass of final blend solids, $m_{B;0}$, is the sum of the entering granulation solids and blend excipients:

$$m_{B;0} = m_{G;0} + m_{B,e;0} \tag{15}$$

Substitution of Eqs. 13–15 into Eq. 12 and multiplying through by the denominator yields:

$$P_{B,f} = P_{G,f} \times \left(\frac{\frac{m_{G,a;0}}{m_{G;0}} \times \left(m_{G;f} + \Delta m_W\right)}{m_{G;f} + m_{B,e;0} + \Delta m_W} \right) \times \left(\frac{m_{G;0} + m_{B,e;0}}{m_{G,a;0}} \right) \tag{16}$$

We can cancel out $m_{G,a;0}$ from the numerator and denominator and divide through by $m_{G;0} + m_{B,e;0}$ to yield

$$P_{B,f} = P_{G,f} \times \frac{\left(m_{G;f} + \Delta m_W\right)/m_{G;0}}{\underbrace{\left(\frac{m_{B,e;0}}{m_{G;0} + m_{B,e;0}} \right)}_{\equiv x_{\text{Extra}}} + \left(\frac{m_{G;f} + \Delta m_W}{m_{G;0} + m_{B,e;0}} \right)} \tag{17}$$

where we have defined x_{Extra} as the fraction of solids added extragranularly. Note that, if no extragranular excipients are added, $m_{B,e;0}=0$, Eq. 17 reduces to $P_{B,f}= P_{G,f}$, as it should.

Dividing the numerator and denominator by $(m_{G;g} + \Delta m_w)/m_{G;0}$ yields:

$$P_{B,f} = \frac{P_{G,f}}{\left(\frac{x_{\text{Extra}}}{\left(m_{G;f} + \Delta m_W\right)/m_{G;0}} \right) + \underbrace{\left(\frac{m_{G;0}}{m_{G;0} + m_{B,e;0}} \right)}_{\equiv 1 - x_{\text{Extra}}}} \tag{18}$$

As in the analysis for the granules, we can write $(m_{G;g} + \Delta m_w)/m_{G;0}$ in terms of known quantities using Eqs. 3, 5, and 7 and the definitions of $L_{G,R}$ and $L_{G,SP}$, yielding:

$$P_{B,f} = \frac{P_{G,f}}{\left(\frac{x_{\text{Extra}}}{\left(1 - L_{G,R} - L_{G,SP}\right) \times (1 + \Delta\text{LOD})} \right) + \underbrace{\left(1 - x_{\text{Extra}}\right)}} \tag{19}$$

Noting that $L_{G,R}$, $L_{G,SP}$, and ΔLOD are all generally <<1, utilizing the Taylor series expansion $1/(1-x) \cong 1 + x$ for x<<1, and neglecting second- and higher-order terms (*e.g.*, O(ΔLOD$\times L_{G,R}$)), Eq. 19 can be approximated as:

$$P_{B,f} \cong P_{G,f} \times \left(1 - x_{\text{Extra}} \times \left(L_{G,R} + L_{G,SP} - \Delta\text{LOD}\right)\right) \tag{20}$$

Since x_{Extra}, $L_{G,R}$, and $L_{G,SP}$ are all $\geq$0, Eq. 20 shows that the mean blend potency will usually be lower than the potency of the granulation. This is because the amount of extragranular excipients added to the milled granules is not reduced to account for losses of the potent material in prior processing steps. The only exception is the unlikely case where $\Delta\text{LOD} > (L_{G,R} + L_{G,SP})$, which corresponds to the increase in mass of the granules relative to the extragranular excipients leading to an increase in the potency of the blend relative to the granules. However, as shown below, the final potency of the blend will still likely be <100% LC.

Substituting in the expression for $P_{G,f}$, Eq. 11, yields:

$$P_{B,f} = \left(1 - L_{G,SP} \times \left(P_{G,SP} - 1\right) - \Delta\text{LOD}\right) \times \left(1 - x_{\text{Extra}} \times \left(L_{G,R} - L_{G,SP} + \Delta\text{LOD}\right)\right) \tag{21}$$

Expanding and, as before, neglecting higher-order terms yields:

$$P_{B,f} = 1 - \underbrace{\left(\left(x_{\text{Extra}} + P_{G,SP} - 1\right) \times L_{G,SP}\right)}_{\text{Effect of mass loss durying drying}} - \underbrace{\left(\left(x_{\text{Extra}}\right) \times L_{G,R}\right)}_{\text{Effect of regular potency mass losses}} - \underbrace{\left(\left(1 - x_{\text{Extra}}\right) \times \Delta\text{LOD}\right)}_{\text{Effect of net water gain}} \tag{22}$$

If we define blend potency reduction as the potency of the blend relative to the theoretical value of 1 (=100% LC), Eq. 22 can be rewritten as:

$$\Delta P_{B,f} = \underbrace{\left(\left(x_{\text{Extra}} + P_{G,SP} - 1\right) \times L_{G,SP}\right)}_{\text{Effect of mass loss durying drying}} + \underbrace{\left(\left(x_{\text{Extra}}\right) \times L_{G,R}\right)}_{\text{Effect of regular potency mass losses}} + \underbrace{\left(\left(1 - x_{\text{Extra}}\right) \times \Delta\text{LOD}\right)}_{\text{Effect of net water gain}} \tag{23}$$

In Eq. 23, we see that blend potency decreases linearly with both water gain and each of the two types of mass loss and the effects are additive. The first two terms on the right-hand side of the equation are always negative, meaning that mass losses during processing always reduce the potency of the final blend. The final term can be either negative or positive, depending if the final LOD of the material leaving the drier is higher or lower than that of the incoming dry materials.

Note that Eq. 23 is independent of the target mass fraction of API in the final blend, $x_{B,a;0}$. The target API fraction only enters the equation indirectly through $P_{G,SP}$, the potency of any subpotent or superpotent material lost during processing "relative" to the target potency. For example, if pure API was lost during processing, $P_{G,SP}$ would be 2,000%, 200%, or 111%, for $x_{B,a;0}$=5%, 50%, or 90%, respectively.

DISCUSSION

Equation 23 describes the final blend potency reduction, $\Delta P_{B;f}$, as a function of five independent variables: x_{Extra}, $P_{G,SP}$, $L_{G,SP}$, $L_{G,R}$, and ΔLOD. In general, the effect of the loss of representative potency material $L_{G,R}$ will be much smaller than that of the other variables. This is because the loss of "regular potency" solids prior to blending only affects the total blend potency due to "dilution". Specifically, because, for this example, the weight of non-potent extragranular excipients added during blending is not adjusted downward to account for pre-blend mass losses, it results in a decreased ratio of "active" granules to non-potent extragranular excipients. Note that, if there are no extragranular excipients (x_{Extra}=0), then we can see that $L_{G,R}$ will have no effect on $\Delta P_{B,f}$.

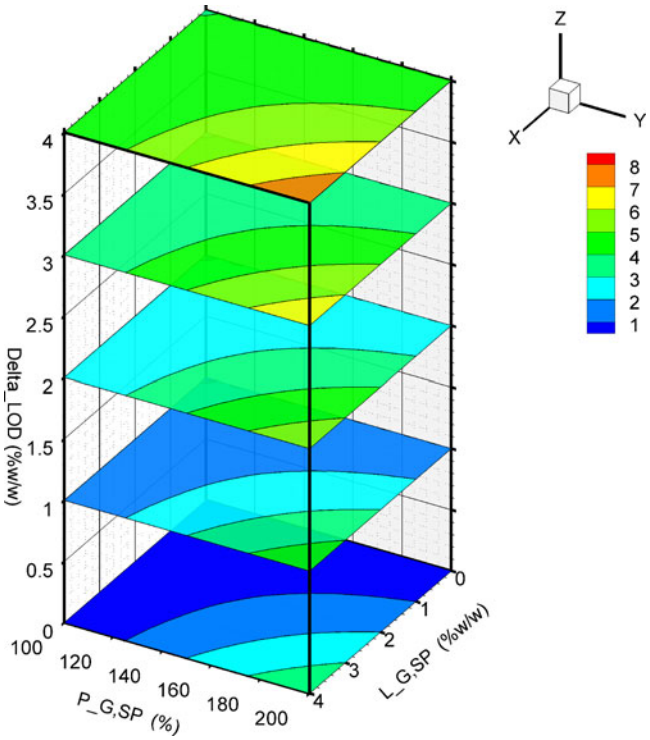

Fig. 2. Reduction in final blend potency, $\Delta P_{B;f}$ $x_{\text{Extra}}=0$. Data sliced to show constant values of ΔLOD. Key: Delta_LOD≡ΔLOD; P_G,SP≡$P_{G,SP}$; L_G,SP≡$L_{G,SP}$

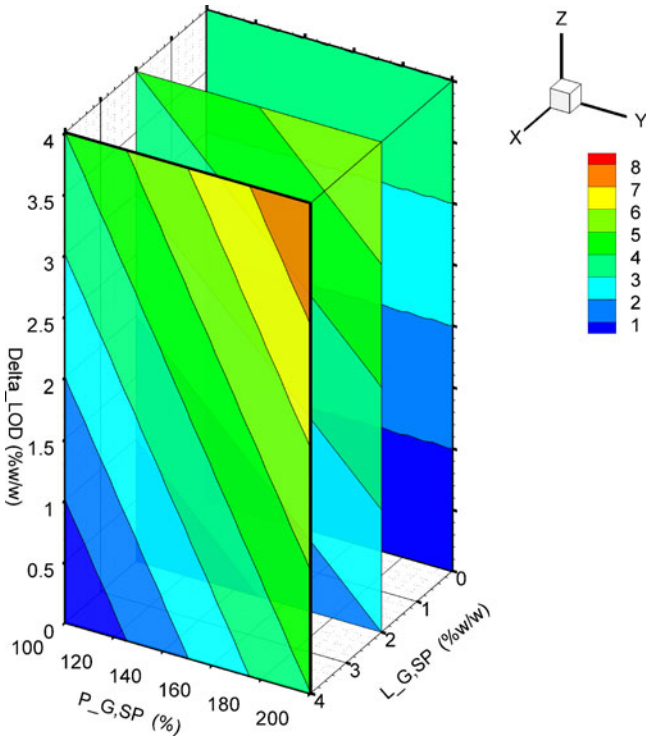

Fig. 3. Reduction in final blend potency, $\Delta P_{B;f}$, for x_{Bxtra} $x_{\text{Extra}}=0$. Data sliced to show constant values of $L_{G,SP}$. KEY: Delta_LOD≡ΔLOD; P_G,SP≡$P_{G,SP}$; L_G,SP≡$L_{G,SP}$

To quantify this, consider a system with $x_{\text{Extra}}=10\%$ *w/w* and $P_{G,SP}=150\%$ LC. Inserting these values into Eq. 23 yields

$$\Delta P_{B,f} = \left(\underbrace{(0.9 \times \Delta\text{LOD})}_{\text{Effect of net water gain}} + \underbrace{(0.6 \times L_{G,SP})}_{\substack{\text{Effect of high-potency} \\ \text{mass losses (i.e.-duringdrying)}}} + \underbrace{(0.1 \times L_{G,R})}_{\substack{\text{Effect} \\ \text{pre-blend masslosses}}} \text{ of other} \right) \tag{24}$$

For this case, each of the following will decrease the potency of the final blend 1% LC: (a) net granulation/drying water gain of 1.1% *w/w*, (b) high-potency mass loss (*i.e.*, during drying), $L_{G,R}$ of 1.7% *w/w*, and (c) regular potency mass losses, $L_{G,R}$, of 10% *w/w*. Although the first two may reasonably occur during drug product manufacture, the latter case will not occur in a well-controlled process. Hence, we will neglect the effect of $L_{G,R}$ on final blend potency for the subsequent discussion.

To better visualize the predictions of Eq. 23, we have plotted it in Figs. 2, 3, 4, 5, 6, and 7 as a function of: (1) ΔLOD, the change in solids water content, (2) $L_{G,SP}$, the mass percent of super or subpotent solids lost prior to blending, and (3) $P_{G,SP}$, the average potency of the super-potent or subpotent material losses relative to the theoretical dried granule potency. The variable ranges are $0 \le \Delta LOD \le 4\%$ *w/w*, $0 \le L_{G,SP} \le 4\%$ *w/w*, and $100\% \le P_{G,SP} \le 200\%$ LC. Two values of the mass fraction of extragranular solids added, x_{Extra}, were used: 0 and 25% *w/w*. We have used $L_{G,R}=0$ since, as discussed in the prior paragraph, this variable has a small effect on the final blend potency. For $x_{\text{Extra}}=0$, Figs. 2, 3, and 4 show the data sliced through the constant ΔLOD, constant $L_{G,SP}$, and constant $P_{G,SP}$ planes, respectively. For $x_{\text{Extra}}=25\%$ *w/w*, the corresponding plots are shown in Figs. 5, 6, and 7.

Over the range of variables studied, ΔLOD has the largest effect on reducing the blend potency. As can be seen from Eq. 23, the effect is proportional to $(1-x_{\text{Extra}})\times\Delta\text{LOD}$, so a 1% *w/w* increase in ΔLOD will decrease the final blend potency up to 1% LC. Hence, for $x_{\text{Extra}}=0$ (Figs. 2, 3, and 4) and $x_{\text{Extra}}=25\%$ *w/w* (Figs. 5, 6, and 7), each 1% increase in ΔLOD decreases the blend potency 1% LC and 0.75% LC, respectively. Note that this effect is independent of $L_{G,SP}$ and $P_{G,SP}$.

When no extragranular excipients are added ($x_{\text{Extra}}=0$), the blend potency reduction is only a function of the product of $L_{G,SP}$ and $P_{G,SP}-1$, not the two variables independently, as shown in Fig. 2. In other words, if the material leaving the dryer is not superpotent ($P_{G,SP}=100\%$ LC), there will be no blend potency reduction, regardless of the amount of material

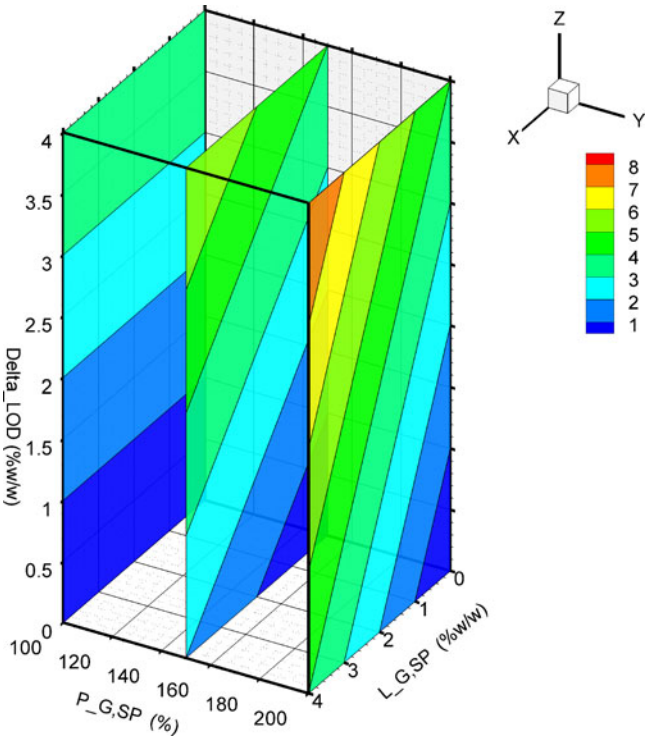

Fig. 4. Reduction in final blend potency, $\Delta P_{B;f}$, for x_{extra}=0. Data sliced to show constant values of $P_{G,SP}$. KEY: Delta_LOD≡ΔLOD; P_G,SP≡$P_{G,SP}$; L_G,SP≡$L_{G,SP}$

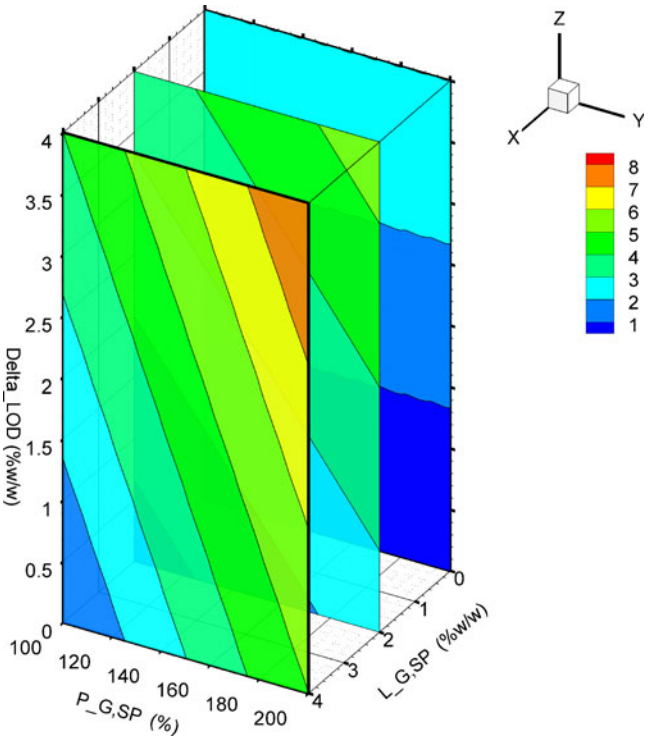

Fig. 6. Reduction in final blend potency, $\Delta P_{B;f}$, for x_{Bxtra}=25% *w/w*. Data sliced to show constant values of $L_{G,SP}$. KEY: Delta_LOD≡ ΔLOD; P_G,SP≡$P_{G,SP}$; L_G,SP≡$L_{G,SP}$

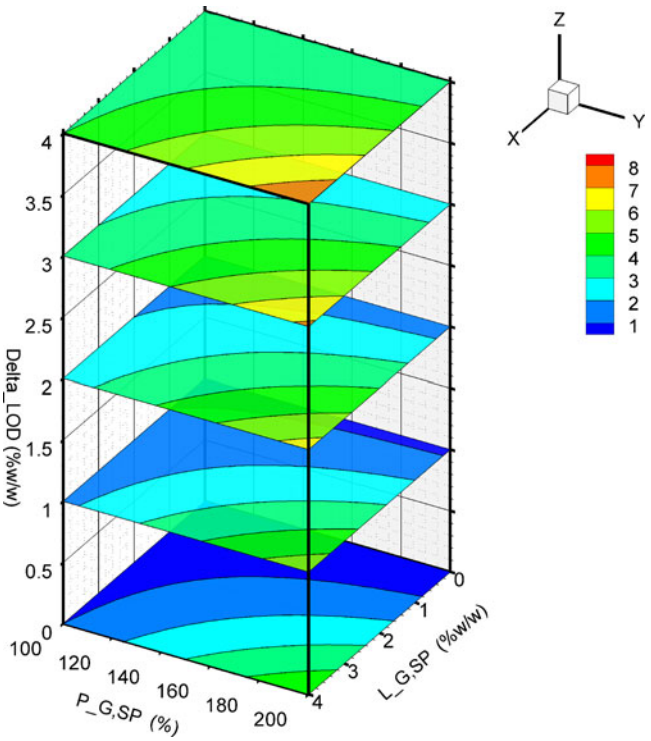

Fig. 5. Reduction in final blend potency, $\Delta P_{B;f}$, for x_{Extra}=25% *w/w*. Data sliced to show constant values of ΔLOD. KEY: Delta_LOD≡ ΔLOD; P_G,SP≡$P_{G,SP}$; L_G,SP≡$L_{G,SP}$

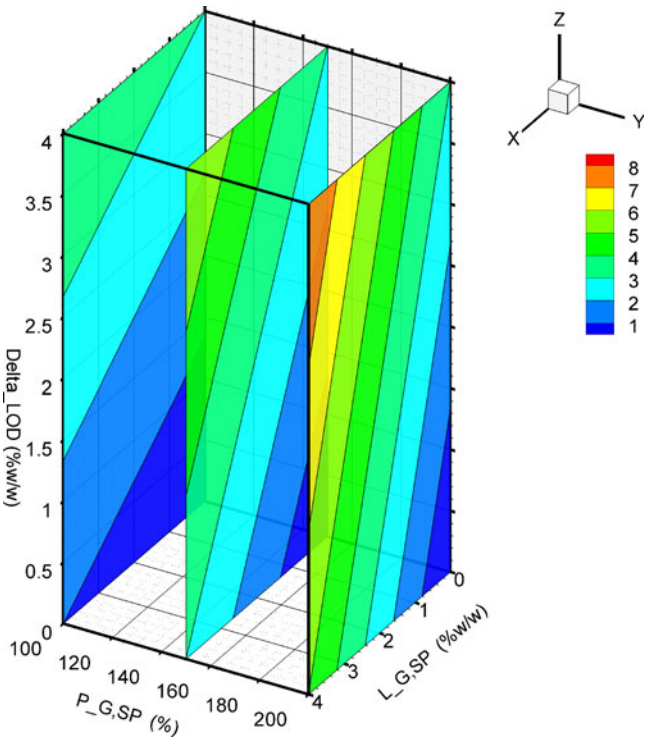

Fig. 7. Reduction in final blend potency, $\Delta P_{B;f}$, for x_{Extra}=25% *w/w*. Data sliced to show constant values of $P_{G,SP}$. KEY: Delta_LOD≡ ΔLOD; P_G,SP≡$P_{G,SP}$; L_G,SP≡$L_{G,SP}$

lost during drying, $L_{G,SP}$. This is illustrated most clearly by looking at the $P_{G,SP}$=100% LC plane in Fig. 4. Similarly, even if the material leaving the drying is superpotent, $P_{G,SP}$>100% LC, and if the amount is insignificant, $L_{G,SP}\approx 0$, there will be no reduction in blend potency. This is illustrated most clearly by looking at the $L_{G,SP}$=0 plane in Fig. 3. Hence, in these cases, blend potency reduction is determined only by ΔLOD.

However, when extragranular excipients are added (x_{Extra}>0), and if $L_{G,SP}$>0, even if $P_{G,SP}$=100% LC, there may be a reduction of blend potency. This can be seen from the $x_{\text{Extra}}\times L_{G,SP}$ term in Eq. 23. This is illustrated most clearly by looking at the $P_{G,SP}$=100% LC plane in Fig. 7. However, the effect is relatively small: even at x_{Extra}=25 % and $L_{G,SP}$=4%, the blend potency reduction is only 1% LC.

The fraction of solids added extragranularly, x_{Extra}, has the smallest effect on blend potency reduction. It does not reduce blend potency by itself, but only if either $L_{G,SP}$ and/or ΔLOD are positive, since x_{Bxtra} only appears as a product with these terms in Eq. 23. The interaction with $L_{G,SP}$ was discussed in the preceding paragraph. The interaction with ΔLOD is counterintuitive: When ΔLOD is positive, x_{Extra} results in a reduction of the rate that blend potency decreases with increasing ΔLOD. This is because a ΔLOD>0 increases the mass of the potent granules relative to the non-potent extragranular excipients. However, the total effect of increasing ΔLOD is still to monotonically decrease blend potency (see the term $(1-x_{\text{Extra}})\times\Delta$LOD in Eq. 23).

Note again that we have assumed that the mass of added extragranular solids is not adjusted downward to account for mass losses through blending. However, even if the mass were adjusted, it would not necessarily eliminate the blend potency reduction. For example, consider a situation where the increase in milled granule mass due to net LOD gain exactly counterbalances the mass loss of superpotent material. In this case, the mass of the milled, dried granules would equal the theoretical weight, so there would be no reduction in the mass of extragranular excipients. However, Eq. 23 shows that since both $L_{G,SP}\times(x_{\text{Extra}}+P_{G,SP}-1)$ and $\Delta LOD\times(1-x_{\text{Extra}})$ are positive, the blend potency is still reduced.

CONCLUSIONS

The analysis shows the importance of avoiding net water gain during the production of an active pharmaceutical blend if one wishes to avoid a reduction in blend potency, as each 1% gain in LOD will decrease the potency of the final blend up to 1%LC. The effect of pre-blend solids losses on the final blend potency increases with their degree of superpotency.

Although written for wet granulation, the developed theory is applicable for any drug product manufacturing process: (1) where the primary sources of potency loss are net water gain and/or mass losses and (2) that can be divided into two or less groups of unit operations. If there are two, the last must be the addition of non-potent excipients. For example, the theory can also be applied to direct compression and roller compaction. Wet granulation was chosen because it is a relatively general case, being more likely to have water gain and/or loss of superpotent material during processing. Note that although we have used aqueous granulation as an example, for a solvent-based process the effect of residual solvent mass would be to dilute potency in a way quantitatively the same as ΔLOD.

By quantitatively relating potency losses to measurable material quantities, the analysis provides a rational method to set the process design space to eliminate potency losses. When the process design space to eliminate potency losses does not overlap with the design space to yield a blend with acceptable processability, the model provide a scientific understanding of the sources of loss and, hence, a stronger justification for the necessary API overage.

APPENDIX

The loss-on-drying (LOD) of a sample is defined as the mass of water, m_W, divided by the total sample mass, m_T.

$$\text{LOD} \equiv \frac{m_W}{m_T} \tag{A1}$$

Where m_T is defined as the sum of m_W and the mass of solids, m_S.

$$m_T \equiv m_W + m_S \tag{A2}$$

Combing Eqs. A1 and A2 and solving for m_W yields

$$m_W = m_S \times \frac{\text{LOD}}{1-\text{LOD}} \tag{A3}$$

We wish to determine the mass change of a material as it transitions from LOD_1 to LOD_2. In this situation, m_W and m_T change, but m_S does not. Using Eq. A3 results in

$$m_{W1} = m_S \times \frac{\text{LOD}_1}{1-\text{LOD}_1} \tag{A4}$$

and

$$m_{W2} = m_S \times \frac{\text{LOD}_2}{1-\text{LOD}_2} \tag{A5}$$

Hence, the change in mass, Δm, is

$$\Delta m \equiv m_{W2} - m_{W1} = m_S \times \left(\frac{\text{LOD}_2}{1-\text{LOD}_2} - \frac{\text{LOD}_1}{1-\text{LOD}_1}\right) \tag{A6}$$

When LOD_1, $\text{LOD}_2 << 1$, Eq. A6 reduces to

$$\begin{aligned}\Delta m &\equiv m_{W2} - m_{W1} = m_S \times (\text{LOD}_2 - \text{LOD}_1)\\ &= m_S \times \Delta\text{LOD}\end{aligned} \tag{A7}$$

The only unknown in Eq. A7 is the mass of solids, m_S. To determine this, Eqs. A1 and A2 can be combined and manipulated to an expression for m_S in terms of m_T and LOD, both of which can be determined experimentally.

$$m_S = m_T \times (1-\text{LOD}) \tag{A8}$$

Note that m_T is a function of LOD, such that Eq. A8 should always yield the sample value of m_S regardless of the value of LOD. Stated another way, LOD changes the mass of water in the sample, but not the mass of solids. However, for

LOD<<1, which has already been assumed earlier in our derivation, Eq. A8 reduces to $m_S \cong m_T$ Substitution into Eq. A7 yields

$$\Delta m \cong m_T \times \Delta\text{LOD} \tag{A9}$$

Equation A9 can be used to determine the mass change of a process intermediate due to a change in the water content. It can also be used to normalize the mass of process losses with a given LOD to what the mass would be if the process losses were at the same LOD as the dry solids loaded into the granulator.

For some situations, either the beginning or ending, LOD will not be <<1. For example, if one measured the mass of the wet material losses left in the granulator bowl, this LOD would likely not satisfy this condition. For this situation, a combination of Eqs. A6 and A8, neither which utilize the assumption LOD<<1, could be used to convert the ΔLOD to Δm.

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