An alternative approach to adjustment of the level of incorporation of boundary lubricants to accommodate changes in granule or blend characteristics.

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ABSTRACT

A method is proposed whereby the determination of the level of incorporation of a boundary lubricant is based on the surface area of the blend or granulation and the shape of the lubricant particles. This is a more logical approach to the lubrication of blends and granulations for the manufacture of solid oral dosage forms than the percentage by weight approach that has traditionally been used. Equations are provided to allow the adjustment of the level of incorporation of the boundary lubricant based on the variation in the surface area of the granulation or blend. This method has a potential application in the manufacture of solid oral dosage forms by both batch and continuous processing. The concept of lubricant coverage is relevant to the development of solid oral dosage forms using Quality by Design principles, since certain changes in the granulation or blend characteristics on scale-up would be compensated for, and the use of grade bracketing strategies would be facilitated.

KEY WORDS: Blending, excipients, lubrication, mannitol, microcrystalline cellulose, sodium starch glycolate, surface area

INTRODUCTION

Lubrication of capsule and tablet blends

Lubricants are added to a pharmaceutical powder or granule blend to facilitate the manufacture of tablets or capsules. Lubricants are generally considered to have a balance of four functions i.e., (1) to reduce friction during powder consolidation and compaction, (2) to facilitate powder flow, (3) to reduce sticking to punch faces, and (4) to facilitate ejection of the tablet from the die, or the transfer of the capsule plug into the capsule body. Different lubricants may show a different balance of these four functions. Tablet lubricants have been grouped according to how they perform. Boundary lubricants (e.g. magnesium stearate) have a polar head and organic tail and typically do not melt during compaction. Fluid-film lubricants (e.g. hydrogenated vegetable oil, type 1), by contrast, melt during compaction to form a thin film that coats surfaces and thereby reduces friction, etc. On the removal of the compaction pressure fluid–film lubricants re-solidify, and thus are said to have auxiliary binding properties.

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The addition of the lubricant to the final blend prior to compaction or encapsulation has traditionally been according to a fixed percentage of the total blend weight. Lubrication has long been recognized as a surface phenomenon (1, 2), and granule and blend characteristics, including particle size distribution and thus surface area, will vary from batch to batch. The surface area of the lubricant can also vary, which has been reported to change the characteristics of tablets produced using magnesium stearate from different sources (3).

This traditional approach to lubrication (i.e. one level fits all by weight) is not optimal, or logical. In addition, many boundary lubricants including magnesium stearate, calcium stearate and zinc stearate are hydrophobic and capable of retarding dissolution and/or disrupting particle-particle bonding during compaction if they are over blended (4). Under lubrication may also lead to problems during tablet compaction including 'dragging' in the dies (higher than normal ejection forces), poor flow (leading to poor tablet weight control), and sticking to the punches (leading to poor weight control and poor appearance).

There is also a likelihood that the characteristics of the lubricant particles themselves will change, for example, particle size and particle size distribution, and thus the surface area that can be covered sufficiently by a given weight of the lubricant.

It should be noted that there are hydrophilic lubricants available, such as, sodium stearyl fumarate (a boundary lubricant) and e.g. polyethylene glycol 6000 (a fluid film lubricant). However, these lubricants are not panaceas. Sodium stearyl fumarate can be expected to be incompatible with primary amine drugs due to the presence of the olefinic double bond with which the primary amine moiety can form an adduct, analogous to a Michaels addition, and polyethylene glycol 6000 has generally only been used in some effervescent products.

There are literature reports that looked at correlating the level of incorporation of lubricant with granule or blend surface area. Shah and Mlodozeniec (1) investigated the effects of the duration of mixing magnesium stearate with direct compression excipients and equated the observed effects with increased delamination of the magnesium stearate agglomerates with extended mixing, and thus increased coverage of the surface of the other components of the blend.

Tan *et al.* (2) investigated the effects of granule particle size on powder flow using a recording powder flow meter, and also based on variations in tablet weight at different machine speeds using a Betapress tablet machine. They adjusted the level of incorporation of the magnesium stearate to compensate for the differences in surface area of the different granule fractions.

The use of weight or surface area for the assessment of the level of incorporation of magnesium stearate into blends for tableting or encapsulation was also investigated by Frattini and Simioni (3). These authors were able to show that there were differences in the performance of three sources of magnesium stearate. However, when the weight of magnesium stearate added to the blends was adjusted to compensate for the surface area of the magnesium stearate as measured using BET nitrogen adsorption, the results for ejection force, hardness, disintegration and dissolution of a tablet formulation prepared using any of the three sources of magnesium stearate were very similar. Whereas, the simple addition of a fixed percentage of magnesium stearate from the three sources produced considerable differences in those same parameters.

Bavitz and Shiromani (5) also investigated the relationship between the level of incorporation of magnesium stearate and the surface area of a calcium phosphate granulation. These authors were able to establish a relationship between the level of incorporation of a lubricant and the surface areas of the granulation and lubricant. The surface area of the granulation was calculated from the results of sieve analysis. The authors do not indicate how the lubricant surface area was determined.

Based on geometric first principles, this report will further explore the alternative approach to determine the level of incorporation of boundary lubricants into final blends for compaction or encapsulation based on the more logical approach of surface area. Fluid-film lubricants, when used in the manufacture of tablets melt, or partially melt under the pressures encountered during compaction. As such, further considerations, beyond those discussed in this report, will likely apply.

There is a reasonable assumption that, for boundary lubricants to function, they should be 'attached' to (i.e., adsorbed onto) the external surface of the granules. Thus, the granule particles can be considered to 'carry' the lubricant particles as a 'payload'. In order for the lubricant to function satisfactorily, there should be a sufficient proportion of the surface of the granules covered with lubricant particles. However, since most boundary lubricants are hydrophobic and can interfere with particle-particle bond formation during consolidation and compaction, it is likely that there will be an optimum coverage, i.e., something considerably less than 100%, since total coverage of the granule surface area would be equivalent to over lubrication, and would likely result in weak tablets, poor disintegration and/or poor dissolution.

Traditionally, the amount of coverage of the granule or blend surface by the lubricant has not been routinely investigated. As stated above, it is common practice to add a fixed quantity of lubricant based on prior experience, typically in the range 0.5 – 1% of the total blend weight for a boundary lubricant.

Since it is well known that lubricants and the lubricant blending process have the potential to adversely impact the pharmaceutical and biopharmaceutical characteristics of finished oral solid dosage forms, it follows that, in the context of the move within the pharmaceutical industry to the adoption of quality by design (QbD) principles, the level of incorporation of the lubricant into the final formulation should be part of at least the initial investigations leading to the formal Design of Experiments (DoE). The approach proposed in this report should be relevant to such studies, and provide a more rational approach to the determination of the level of incorporation of lubricants in blends for the manufacture of solid oral dosage forms.

Particle surface area

In general terms, pharmaceutical granules can be considered as irregular porous composites comprised of several different components, typically the active pharmaceutical ingredient (API) and excipients. The surface area of interest for lubrication purposes is the external surface area (sometimes referred to as the envelop surface area) as shown in Figure 1.

In Figure 1 the external surface is approximated by the dotted circle. In reality, the granule would be three-dimensional and the external surface area would approximate to a sphere. The granule is porous, and the internal surface area of the granule will be included in the determination of surface area by methods such

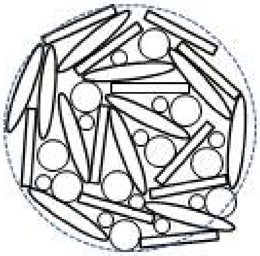

Figure 1 A schematic two-dimensional representation of a pharmaceutical granule.

as BET nitrogen adsorption. The external surface area of a powder can be determined by air permeametry using e.g., either a Lea and Nurse apparatus, or a Rigden apparatus. Alternatively, if the assumption that the granules are spherical(or some other regular shape) is valid, the external surface area can be calculated. For a particle approximating a sphere, the surface area of the particle can be calculated from the particle diameter (strictly, the diameter of the sphere having the same external surface area as the granule). These arguments can be applied to any particle in a blend.

Pharmaceutical powder blends typically are not mono-sized, and there will be a particle size distribution associated with the blend. If the particle size distribution is symmetrical i.e., Gaussian or normal, the mean size could be used. However, most pharmaceutical particle size distributions are not Gaussian, but skewed, e.g., log-normal. For a symmetrical distribution the mean, median and mode coincide. The one parameter that does not change, whether the distribution is Gaussian or log-normal, is the median (d_{50}). Thus even if the distribution is log-normal, or some other non-Gaussian distribution, the median particle size is the particle size that is most appropriate to be used in calculating the external surface area of the granules.

It is common to include additional disintegrants and/or additional fillers in the final blend for tableting or encapsulation. This complicates the calculation of the median particle size, however, it should not prevent the determination of the external surface area by air permeametry. It is also possible to calculate the relevant surface area for multiple component blends by summing the contributions of each component to the total surface area (see later in this report).

LUBRICANT COVERAGE

As discussed above, there will be an optimum level of lubricant for a given batch or product, designated for the purposes of this discussion as lubricant overage (LC). This optimum level represents a balance between sufficient lubrication to be able to manufacture the product, but not too much so as to decrease tablet hardness, increase disintegration, or retard dissolution in an unacceptable manner. In essence, the goal is to maintain a good dissolution (or adequate tablet strength) while obtaining an adequate powder flow, and thus unit weight control, and low ejection force (represented schematically in Figure 2).

The approach discussed in this report is based on the geometry of the blend and lubricant particles. There are certain assumptions inherent to the use of this surface area approach for the determination of the level of incorporation of a boundary lubricant into a pharmaceutical powder and/or granule blend and they include:

- Where the lubricant particles before the addition to the blend present as stacks of lamellae, the size for the purposes of this discussion is that of an individual lamellae.
- The median particle size of the lubricant particles is much smaller than those of the other blend components, with the exception of any added glidant.
- Disc- or plate-like particles are adsorbed flat on the surface of the blend particles. This would be the orientation likely offering maxi-

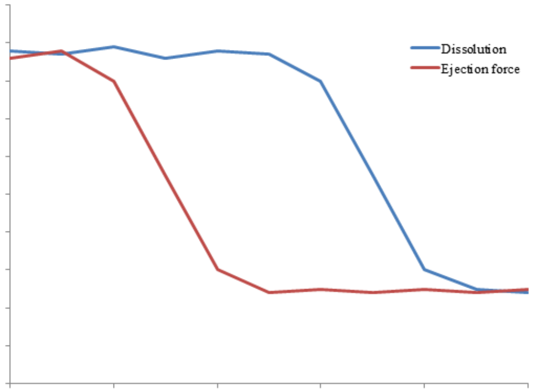

Figure 2 Schematic representation of the balance in the level of incorporation of a lubricant into a solid oral dosage form.

mum particle-particle interaction, but cannot be guaranteed. However, given the nature of the powder blending process, lubricant particles adsorbed on their edge may not have a strong enough particle-particle adhesion to remain attached to the blend particles due to the shear forces exerted during blending.

- The lubricant particles are not abraded during the blending process. If this happened it would increase the area covered by a given quantity of lubricant beyond that anticipated from the geometry of the lubricant particles added to the blend. Film formation has been shown for magnesium stearate (4). However, the nature of the film, individual lamellae or lamellar fragments, was not investigated.
- The lubricant particles are able to adsorb onto the blend particles and/or granules, i.e. the lubricant-particle interaction is sufficiently strong.
- All the lubricant particles in the amount added are able to adsorb onto the surface of the blend particles or granules.

The assumptions listed may not be fully valid. However, in the context of a typical blending process used for the lubrication of pharmaceutical solid oral dosage forms, and having regard for the amount of boundary lubricant typically added to such blends (0.5 – 1% by weight), many of the assumptions may be acceptable.

A further objection to the approach discussed in this paper is that the boundary lubricant particles will adsorb differently onto the different blend components. This may be the case, however, the small boundary lubricant particles do seem to adsorb onto most pharmaceutical powders. This has been confirmed using triboelectrification (6).

The concept of lubricant coverage is similar to the carrier payload concept proposed by van Veen et al. (7). However, the application discussed in this report is somewhat different and the equations also differ.

The lubricant coverage (*LC*) for a given formulation can be calculated as follows:

$$LC = \frac{Total\ projected\ surface\ area\ \ of\ lubricant\ particles}{Total\ available\ surface\ area\ \ of\ \ blend\ particles} \qquad \text{Eq. 1}$$

If the assumption that the blend particles are approximately spherical is valid, the surface area of a spherical particle ($SA_{particle}$) can be calculated using a standard geometric formula:

$$SA_{particle} = 4\pi . \mathrm{r}^{\mathbf{2}}_{particle} = \pi \, \mathrm{d}^{\mathbf{2}}_{particle} \qquad \text{Eq. 2}$$

Where, $r_{particle}$ is the radius and $d_{particle}$ is the diameter of the spherical particle. If n_{blend} is the number of particles in a given weight of blend, then the total surface area in that weight of powder or blend ($SA_{Total\ blend}$) is:

$$SA_{Total\ blend} = \pi d^{2}_{blend}\ .\ n_{blend} \qquad \text{Eq. 3}$$

Lubricant particle shape

The projected area of the lubricant particles depends on their shape. Theoretically, boundary lubricant particles can be of any shape. However, the most common shapes in the author's experience approximate to spheres, circular discs or hexagonal plates.

The maximum coverage over an area, such as the surface area of a sphere, can be obtained using particles that fit together precisely, i.e., regular triangular, square or hexagonal plates that cover the entire surface in a layer one particle thick. The maximum coverage by circular discs will use the same number of particles as for hexagonal particles, but there will be gaps because the spheres do not fit together precisely (see Figure 3). The disc-shaped particles will be of a maximum size that just fits in the area of the hexagon as shown by the dashed circles in Figure 3.

The projected surface area calculation for both spheres and circular discs is the same, assuming

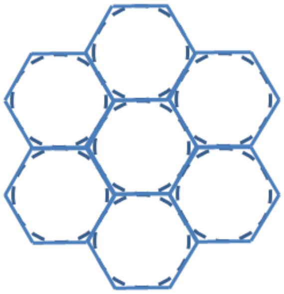

Figure 3 Surface packing of hexagonal and circular particles.

that the lubricant discs lie flat on the surface of the granules, i.e. the area of a circle of a given radius:

$$SA_{Proj\ lub} = \pi r^2_{lub} = \pi \frac{d^2_{lub}}{4} \qquad \text{Eq. 4}$$

Where r_{lub} is the projected surface area radius of the lubricant particle, and d_{lub} is the projected surface area diameter. If n_{lub} is the number of lubricant particles in the given weight of lubricant incorporated into the final blend, then the total projected surface area of the lubricant incorporated into the given weight of blend is:

$$SA_{Proj\ lub\ total} = \pi \frac{d^2_{lub}}{4} . n_{lub} \qquad \text{Eq. 5}$$

The surface area of a hexagon is given by:

$$A = 2.598 . r^2 = 2.598 \frac{d^2}{4} \qquad \text{Eq. 6}$$

Where, for a regular hexagon r is the length of one side, and d_{lub} is the distance between opposite corners of the hexagon. Thus for a hexagonal lubricant particle, the projected surface area is:

$$SA_{Proj\ lub} = 2.598 \frac{d^2_{lub}}{4} \qquad \text{Eq. 7}$$

If n_{lub} is the number of lubricant particles to be incorporated into the given weight of final blend, then the total projected surface area of the lubricant incorporated into the given weight of blend is:

$$SA_{Proj\ lub\ Total} = 2.598 \frac{d^2_{lub}}{4} . n_{lub} \qquad \text{Eq. 8}$$

For circular lubricant particle, either disc or sphere, lubricant coverage may be calculated using Equation 1. Assuming the disc-shaped particles lie flat on the surface of the blend particles, we get:

$$LC = \frac{\pi \frac{d^2_{lub}}{4} . n_{lub}}{\pi d^2_{blend} \cdot n_{blend}} \qquad \text{Eq. 9}$$

Similarly for hexagonal particles (assuming the particles are all aligned flat against the surface of the granule or blend particles):

$$LC = \frac{2.598 \frac{d^2_{lub}}{4} . n_{lub}}{\pi d^2_{blend} \cdot n_{blend}} \qquad \text{Eq. 10}$$

Thus if we know the median lubricant particle size, median blend particle size and the numbers of lubricant and blend particles we can calculate the LC for a particular application. If we know of an application that has a good balance of lubricant characteristics, and we can measure the salient parameters for both the lubricant and the granulation or blend, we can determine the LC, but more importantly, we can determine the change in lubricant level that will be required to maintain the LC if the characteristics of the lubricated blend are to be maintained. For example, for a circular disc or spherical particle we can calculate as follows:

$$\frac{\pi \frac{d^2_{lub1}}{4} \cdot n_{lub1}}{\pi d^2_{blend1} \cdot n_{blend1}} = LC = \frac{\pi \frac{d^2_{lub2} \cdot n_{lub2}}{4}}{\pi d^2_{blend2} \cdot n_{blend2}} \quad \text{Eq. 11}$$

Similarly for hexagonal discs assuming that all lubricant particles are adsorbed flat on the surface of the blend or granulation particles, we get:

$$\frac{2.598 \frac{d^2_{lub1}}{4} \cdot n_{lub1}}{\pi d^2_{blend1} \cdot n_{blend1}} = LC = \frac{2.598 \frac{d^2_{lub2} \cdot n_{lub2}}{4}}{\pi d^2_{blend2} \cdot n_{blend2}} \quad \text{Eq. 12}$$

Weight of material

The number of particles is not a convenient means to determine the quantity of lubricant to be added. It is more convenient to calculate the mass of lubricant to be added to a particular blend.

The weight of an individual particle can be determined from its volume and particle density. In the cases of spheres, circular discs and hexagonal plates, for a given 'diameter' the particle volumes will be different.

The volume of a sphere is given by:

$$v = \frac{3}{4} \pi r^3 = \frac{4}{3} \pi \frac{d^3}{8} \quad \text{Eq. 13}$$

Where, r and d are the particle radius and diameter respectively. Thus the weight of an individual spherical particle is:

$$m = \frac{4}{3} \pi \frac{d^3}{8} . \rho \quad \text{Eq. 14}$$

Where, m is the mass of the particle and ρ is the particle density.

The volume of a circular disc is the product of its surface area and thickness (l). Thus the weight of a single circular, disc-shaped particle is:

$$m = \pi \frac{d^2}{4} . l . \rho \quad \text{Eq. 15}$$

Similarly for a hexagonal, plate-shaped particle, the weight of an individual particle is:

$$m = 2.598 \frac{d^2}{4} . l . \rho \quad \text{Eq. 16}$$

Similar equations can be developed for other particle shapes.

Since we can calculate the mass of an individual particle, it follows that if we know the weight of material added, we can calculate the number of particles in a given weight of material, and if we know the numbers of different particles we can determine the lubricant coverage. Thus, for example, for a lubricant consisting of hexagonal, plate-like particles, the number of particles in a given weight M_{lub} is:

$$n_{lub} = \frac{M_{lub}}{2.598 \frac{d^2_{lub}}{4} . l_{lub} . \rho_{lub}} \quad \text{Eq. 17}$$

And for a granule consisting of approximately spherical particles and having a weight of M_{blend}, then the number of particles is:

$$n_{blend} = \frac{M_{blend}}{\frac{3}{4} \pi \frac{d^3_{blend}}{8} . \rho_{blend}} \quad \text{Eq. 18}$$

Substituting equations 17 and 18 into equation 10, cancelling through and rearranging, we get:

$$LC = \frac{M_{lub}}{l_{lub} . \rho_{lub}} . \frac{d_{blend} . \rho_{blend}}{6. M_{blend}} \quad \text{Eq. 19}$$

If we know the lubricant coverage we want to achieve, and assuming that all lubricant particles are adsorbed flat on the surface of the granulation/blend particles, we can calculate the quantity of lubricant to incorporate in a new blend or granulation according to:

$$\frac{M_{lub1}}{l_{lub}\cdot\rho_{lub1}}.\frac{d_{blend1}\cdot\rho_{blend1}}{6.M_{blend1}}=LC =\frac{M_{lub2}}{l_{lub2}\cdot\rho_{lub2}}.\frac{d_{blend2}\cdot\rho_{blend2}}{6.M_{blend2}} \qquad \text{Eq. 20}$$

We can derive similar equations for both lubricant coverage and for the calculation of the amount of lubricant required to maintain a certain lubricant coverage for both spherical and circular, disc-shaped lubricant particles, again assuming that the blend particles are approximately spherical.

For spherical lubricant particles, assuming approximately spherical granulation or blend particles, the equivalent equations are (see Equations 2 and 3 in Appendix A):

$$LC=\frac{M_{lub}}{4\ .\ d_{lub}.\ \rho_{lub}}=\frac{d_{blend}\cdot\rho_{blend}}{M_{blend}} \qquad \text{Eq. 21}$$

and:

$$\frac{M_{lub1}}{4.\,d_{lub1}\cdot\rho_{lub1}}.\frac{d_{blend1}\cdot\rho_{blend1}}{M_{blend1}}=LC \quad \frac{M_{lub2}}{4.\,d_{lub2}\cdot\rho_{lub2}}.\frac{d_{blend2}\cdot\rho_{blend2}}{M_{blend2}} \qquad \text{Eq. 22}$$

For circular, disc-shaped lubricant particles, assuming approximately spherical granulation of blend particles, the equivalent equations are (see Equations 2 and 3 in Appendix B):

$$LC=\frac{M_{lub}}{l_{lub}\cdot\rho_{lub}}.\frac{d_{blend}\cdot\rho_{blend}}{6.M_{blend}} \qquad \text{Eq. 23}$$

and:

$$\frac{M_{lub1}}{l_{lub1}\cdot\rho_{lub1}}.\frac{d_{blend1}\cdot\rho_{blend1}}{6.M_{blend1}}=LC= \quad \frac{M_{lub2}\cdot}{l_{lub2}\cdot\rho_{lub2}}.\frac{d_{blend2}\cdot\rho_{blend2}}{6.M_{blend2}} \qquad \text{Eq. 24}$$

MULTIPLE COMPONENT BLENDS

In the formulation and manufacture of oral solid dosage forms, it is very unusual to have a mono-sized powder that only requires the addition of a lubricant; usually there would be a particle size distribution associated with the powder. As stated above, it is also unusual to have only one blend component besides the added lubricant. Typically, other excipients are added to the final blend, such as a disintegrant or extra filler, possibly also a glidant. In the approach proposed in this paper, the total surface area of the resultant blend is necessary to determine the adjustment, if any, in the amount of lubricant to be added to the final blend in order to maintain the lubricant coverage. To determine the lubricant coverage for the blend, the surface area of each component can be calculated, and its contribution to the overall surface area from the relative amounts of the different components in the formulation. This can be either as a percentage of the blend, for the total blend weight, per gram, or per unit dose. If the physical form of the particles is known, the particle density, the particle diameter (or other appropriate dimension for non-round particles), and the particle thickness for disc-shaped or plate-like particles, then the contribution of each component to the surface area can be calculated, either as a percentage of the blend, or by weight of components in the final blend.

Worked examples

Consider the following direct compression formulation, and let us assume for the purposes of this example that the individual components are approximately spherical:

	mg/unit
Active Pharmaceutical Ingredient	10.0
Spray-dried mannitol	40.0
Microcrystalline cellulose PH200	46.0
Sodium starch glycolate	4.0
TOTAL	100.0

It also assumed, from development studies, that the lubricant coverage optimum performance has been determined. The components of the formulation will all have a variability associated with them. For the purposes of this example, we are only interested in the variability in particle size (median, d_{50}) and particle density.

Note that particle density does not necessarily refer to true density. For some materials the particle density and true density may be the same, or similar. However, for other materials where the particles are formed from smaller particles, the particle density is unlikely to be the true density because of the voids within the structure of the particle. Further note that the lubricant has yet to be added and will be extra to the quantities shown above.

The surface area of a spherical particle is given in Equation 2. However, the total surface area of a blend is the sum of the contributions from its components. Taking the example formulation shown above, each of the components will contribute to the total surface area in proportion to their level of incorporation into the mix. From The number of particles for a component is given by Equation 18.

From Equation 3 we know that the surface area contribution of a particular component of the blend is the product of the surface area of an individual particle and the number of particles, i.e. the product of equations 3 and 18. By cancelling through and rearranging, we get:

$$SA_{component} = \frac{6.M_{component}}{d_{component} \cdot \rho_{component}} \quad \text{Eq. 25}$$

and:

$$SA_{Total\ blend} = SA_{c1} + SA_{c2} + SA_{c3} + SA_{c4} \quad \text{Eq. 26}$$

Where: *c1, c2, c3* and *c4* represent components 1, 2, 3 and 4 of the blend, respectively. Thus calculate the surface area of the blend can be calculated, and thus the quantity of lubricant necessary to achieve the desired lubricant coverage.

There are implicit assumptions in all of this i.e., that the lubricant is present as individual particles, and that the lubricant particles, if plates or discs, are positioned flat on the surface of the blend particles. Such assumptions may not always be valid. However, even if this assumption is not valid, it may be of little consequence since we are looking to compare blend surface areas from batch to batch using the same or similar processing, and thus similar shear forces during the blending process (or from processing time to processing time in continuous manufacturing).

The processing may be such that there is insufficient shear, even on scale up in batch processing, to break up lubricant agglomerates further. Thus the effective lubricant coverage would be the same, and any agglomeration would be accounted for in the particular lubricant coverage that had been found optimal during development. It should also be remembered that, even if the lubricant particles are not completely deagglomerated, the net effect would be to possibly require more lubricant than a theoretical analysis would predict. However, that investigation should also have been included during the development studies.

The orientation of the lubricant particles on the surface of the blend particles cannot be guaranteed. However, since the blending process is such that it effectively ensures that the range of orientations will be similar for all blends; this is also accounted for in the optimum lubricant coverage determined during the development studies.

The final question to be answered concerns how the variation in particles dimensions and particle density could impact the lubrication of oral solid dosage forms. Using the example, of the formulation given above, the specifications or anticipated ranges for variation in key parameters could be as shown in Table 1.

Table 1 Particles size and particles density data for the blend components

	d_{50} (specification/anticipated range)	ρ	M (%)
API	30 μm (20 – 40 μm)	1.5	10.0
Spray-dried mannitol (Mannogen EZ)	133 μm (111 – 154 μm)	0.95[a]	40.0
Microcrystalline cellulose (Emcocel LP200)	195 μm (135 – 253 μm)	0.88[b]	46.0
Sodium starch glycolate (Glycolys)	42 μm (30 – 55 μm[c])	0.78	4.0

[a] From Reference (7).
[b] The true density given in the literature (8) is ca. 1.44 g/cm^3. The particle density would be less than that but greater than the tapped density, and would be expected to be less than that for spray dried mannitol. For the purposes of this exercise a value of 0.88 g/cm^3 has been assumed.
[c] Estimated for the purposes of this exercise.

From Equation 25, it can be seen that both the particle diameter and particle density contribute to the surface area. However, since generally, the value for median particle diameter is much larger than that for the particle density, and is likely to exhibit more variation, for simplicity we will consider only the variation in particle size in this example.

Worked example 1

It is further assumed that three batches of the product are to be made and that from the development studies the optimum lubricant coverage was found to be 0.2 (i.e. 20% of the theoretical maximum coverage). For the purposes of this example, for one batch of product, the d_{50} parameters for all the components are in the middle of specification or anticipated range. For the other two batches, one batch is to be made with materials that are at the top end of the specification or anticipated range, and for the third batch each component is at the lower end of the specification or anticipated range. What weight of lubricant, at a LC of 0.2, will be required for each of the three batches?

For the blend composed of materials with d_{50} values at the center of the range we have:

For the API:

$$SA_{API} = \frac{6.M_{API}}{d_{50\,API} \cdot \rho_{API}} = \frac{6\text{x}10}{30\text{x}1.5} = 1.33 \qquad \text{Eq. 27}$$

For the spray-dried mannitol:

$$SA_{man} = \frac{6.M_{man}}{d_{50\,man} \cdot \rho_{man}} = \frac{6\text{x}40}{133\text{x}0.95} = 1.90 \qquad \text{Eq. 28}$$

For the microcrystalline cellulose:

$$SA_{MCC} = \frac{6.M_{MCC}}{d_{50\,MCC} \cdot \rho_{MCC}} = \frac{6\text{x}46}{195\text{x}0.88} = 1.61 \qquad \text{Eq. 29}$$

For the sodium starch glycolate:

$$SA_{SSG} = \frac{6.M_{SSG}}{d_{50\,SSG} \cdot \rho_{SSG}} = \frac{6\text{x}4}{42\text{x}0.78} = 0.73 \qquad \text{Eq. 30}$$

Thus the total surface area from equation 26 is:

$$\begin{aligned} SA_{Total\ blend} &= SA_{API} + SA_{man} + SA_{MCC} + SA_{SSG} = \\ &1.33 + 1.90 + 1.61 + 0.73 = 5.57 \end{aligned} \qquad \text{Eq. 31}$$

Note that the units for the surface areas are not fully standardized i.e., there is a mix of both cm in the density function and μm in the particle dimension. However, since we are only interested in relative numbers to compare surface areas and adjust the quantity of lubricant, as long as all the units for the different types of values are consistent, there is no need to fully standardize the units.

The required surface area for lubrication purposes is thus the product of the total surface area of the blend and the required LC. Equations similar to those for Equations 27 to 31 can also be generated for the blends with materials conforming to the low and high d_{50} values. The results of these calculations are given in Table 2.

Table 2 Surface area contributions for the different components of the blend

	Low d_{50}	Mid-range d_{50}	High d_{50}
API	2.00	1.33	1.00
Spray dried mannitol	2.28	1.90	1.64
Microcrystalline cellulose	2.32	1.61	1.24
Sodium starch glycolate	1.03	0.73	0.56
SA_{Total}	7.63	5.57	4.44
$SA_{Required\ lub}$ (at LC 0.2)	1.53	1.11	0.89

For a lubricant coverage of 0.2 for the blends listed in Table 2 we simply multiply the SA_{Total} values by 0.2. This is then the equivalent surface area coverage for which we need to calculate the required weight of lubricant. Thus, for the blends in this example the SA_{Total} values (at LC 0.2) are also included in Table 2.

For the purposes of this exercise, it is assumed that the lubricant is comprised of hexagonal plates, with the following dimensions: maximum width 8 μm (range 6 – 10 μm) and a thickness of 1 μm, and particle density of 1.11. For simplicity it is further assumed that the same batch of lubricant is used for all three blends. However, the same calculations can be used with different lubricant batches whose particles could be anticipated to vary slightly in size.

For hexagonal plates the required projected surface area of the lubricant particles is given by Equation 8. Combining Equations 8 and 18 and cancelling through, we get:

$$SA_{Required\ lub} = \frac{M_{lub}}{l_{lub} \cdot \rho_{lub}} \qquad \text{Eq. 32}$$

For our purposes, we are interested in the weight of lubricant required (M_{lub}):

$$M_{lub} = SA_{Required\ lub} \cdot l_{lub} \cdot \rho_{lub} \qquad \text{Eq. 33}$$

The value for $SA_{Required\ lub}$ is the area incorporating the extent of lubricant coverage from Table 2. Thus for the three blends listed in Table 2, the quantities of lubricant required to maintain 0.2 LC are:

Low d_{50}	1.70
Medium d_{50}	1.23
High d_{50}	0.99

The difference between the weight of lubricant required for the low d_{50} and medium d_{50} blends is about 38% using the medium d_{50} blend as the norm. There is also a difference of about 20% between the weight of lubricant required for the medium d_{50} and high d_{50} blends. For a formulation that is sensitive to the lubricant level, it is possible that over or under lubrication to such an extent could cause problems during compaction and/or testing of the finished tablets. The approach outlined above would allow for a constant level of incorporation of the lubricant based on surface area, and thus avoiding under- or over-lubrication during routine manufacture of the pharmaceutical product.

Worked example 2

In another likely scenario, during the development of the Design Space (and thus the Control Strategy) as part of the Quality-by-Design (QbD) approach to pharmaceutical formulation development, one of the options to investigate excipient variability is to substitute excipient grades having the properties being investigated on either side of the desired grade

(grade bracketing) (10). In such an investigation, the difference in median particle size will change the external surface area of that component of the blend. For example, the desired grade of an excipient to be incorporated in the final blend is for instance microcrystalline cellulose 90M (d_{50} ca. 110 µm, range 95 – 150 µm), and the attributes to be investigated meant that the bracketing grades would be 50M (d_{50} ca. 60 µm, range 45 – 80 µm) on the smaller particles size and LP 200 on the larger side. Thus there would be a difference in surface area between the three grades. From the calculations presented above, this would mean an approximately 65% difference in the surface area of the blends for the formulation given in the first example above between the 50M and LP200 grades. Using the calculations reported above, and assuming that the other components of the blend were from the same lots, the levels of incorporation of the lubricant in the three blends for the three grades of microcrystalline cellulose to maintain the same LC would be as follows:

50M (PH101)	2.04
90M (PH102)	1.51
LP200 (PH200)	1.23

These data represent differences of about 35% for the change to the 50M grade, and about 19% for the LP200 grade compared to the target grade (90M). The 50M blend would in effect be under-lubricated and the LP200 blend over-lubricated. From the author's experience, a theoretical reduction in the level of the boundary lubricant of about 35% would be of concern. Similarly, a theoretical increase in the level of boundary lubricant of about 20% would also be of concern.

Using the concept discussed in this report of maintaining a certain LC would permit a more efficient investigation of such intentional variations in formulation parameters on the attributes of the finished product by removing the additional variability of the level of lubricant incorporation relative to the grade of the excipient.

DISCUSSION

The worked examples given above were direct compression formulations. The LC concept is also applicable to granulated materials. For a granulation, the granulated material is simply a single component of the final blend with a particle size, particle density and external surface area, regardless of how many components make up the granulation. This reasoning applies whether the granulation is prepared by wet granulation or dry granulation. In the examples given above, the lubricant source and lot, were kept the same. However, the equations developed and used in the examples are also applicable to situations where the lubricant characteristics do change, such as in the investigation reported by Frattini and Simioni (3).

It is envisioned that a major use of the LC concept would be during QbD tablet and capsule formulation development projects to facilitate the transition through formulation design development and scale up. Once the formulation components are decided, the correct LC together with the acceptable range could be determined during early studies using a variety of attributes and methods including compaction, dissolution, breaking strength, ejection force, etc., and the simple calculations provided in this report. Once determined, the LC could then be maintained throughout the development phase and into commercial manufacture. The only proviso being that the effectiveness of the level of incorporation of the lubricant in the blend (ejection force, weight control, breaking strength, dissolution, etc.) should be confirmed on scale up. The application of the LC concept in this manner would remove some of the potential variability seen during scale up, and simplify the Design of Experiments (DoE) used to establish the Design Space and thus justify the Control Strategy.

As experience is gained in the application of the approach to determining the level of incorporation of boundary lubricants described in this report, the LC concept could also be used to decide the initial level(s) of incorporation of lubricant in tablet or capsule blends to be investigated at the start of the formulation design project.

There is still an unanswered question: what difference in LC can be tolerated before problems arise, i.e., how much can the surface area of the main blend components decrease before there is a reduction in dissolution, an increase in disintegration time and/or a decrease in tablet breaking strength, and how much can the surface area of the main components of the blend increase before there is an unacceptable increase in tablet ejection force or capsule plug ejection force? The answer will vary with the particular formulation. Some formulations may be more susceptible to over- or under-lubrication than others. However, it is likely that differences in excess of 20% as shown in the examples above could be anticipated to cause concern.

The determination of LC in the examples given in this report was by calculation from the d_{50} for the different components of the blend and their relative proportions. There are other means by which the LC could be determined, e.g. using a combination of air permeametry and inverse gas chromatography using hydrophilic probes for hydrophobic lubricants. Other techniques could include Raman spectroscopy, NIR spectroscopy, etc.

The first worked example above used the limits of the d_{50} to determine the upper and lower ranges for the blend surface area. As such, this example gives an indication of the maximum range of surface areas that could be anticipated. Obviously, there would likely be a majority of manufactured lots where the blend surface area would be much closer to the center of the range. It can be argued that the traditional weight-based addition of material is satisfactory and should continue to be used. This may well be the case for some formulations. However, for those formulations which are particularly sensitive to the level of the addition of magnesium stearate, the proposed LC concept would help in avoiding unnecessary out of trend investigations and possibly rejections due to problems during manufacture, problems with the results from the release testing, or investigations of reports of poor clinical efficacy. In order to reduce the need for possible adjustments of the weight of boundary lubricant to be added to every batch, depending on the sensitivity of the formulation to the level of boundary lubricant, it should be possible to set a threshold for blend or granulation surface area change within which change was not deemed necessary; for example if the change in surface area was less than ±5%, or perhaps ±10% (depending on the lubricant sensitivity of the particular formulation), the weight of boundary lubricant would not be adjusted.

One further objection may be from a regulatory perspective. Traditionally, the regulatory agencies have favored fixed qualitative and quantitative formulations. Adjusting the level of incorporation of a boundary lubricant based on the surface area of the blend implies formulation flexibility. However, let us consider the changes in the context of the overall formulation. If we take the data from the first worked example above, the level of incorporation of the boundary lubricant were calculated to be as follows:

Low d_{50}	1.67
Medium d_{50}	1.22
High d_{50}	0.98

The differences in the levels of incorporation of the boundary lubricant compared to the medium d_{50} are less that the ±1% of the total formulation permitted under the SUPAC IR Guideline (11), and as discussed above the difference in these blends probably represent the maximum variability that would be seen with this formulation.

There is a move towards continuous manufacture of pharmaceutical finished products, and it is currently investigated for solid oral dosage forms. The LC concept could be applied to continuous processing. The parameters required are the particle density of the particular excipients (for many excipients the variation in this particular parameter can probably be taken to be minimal for a specific excipient grade), median particle size of the excipients (or other appropriate dimensions for non-spherical particle and thickness for disc- or plate-like particles). It may also be possible to measure the median particle size *in situ*. A feed forward mechanism could then adjust the level of incorporation of the lubricant automatically through the process control system. Again the concept of a threshold for change in surface area could be used to reduce the frequency of adjustment of the amount of boundary lubricant added with the concomitant change in tablet compression weight.

In the worked examples presented above, the surface area of the powder or granule blend prior to the addition of the lubricant was calculated from the particle dimensions of the blend components. It is also possible to determine the external (envelope) surface area experimentally, e.g., by air permeametry. The LC concept could also be applied using such data from e.g. Equation 33, or equivalent depending on the shape of the lubricant particles.

The examples presented above were designed to show how the principles of the concept could be applied. It is interesting to note that using LC 0.2 gave levels of incorporation of the boundary lubricant that were on the higher side compared to the traditional levels of incorporation of boundary lubricants in powder or granule blends (0.5 – 1% w/w). This implies that in practice LC at ca. 0.1 – 0.15 may be more appropriate.

The practical application of this concept to formulation development, and QbD projects in particular, remains to be investigated. However, the LC concept does have application beyond lubricants and formulation development.

A further application of the LC concept could be in the investigation of second sources of excipients as part of an excipient supply risk mitigation strategy. An examination of the median particle size and calculation of the appropriate surface area would give an indication of just how interchangeable excipients from different sources might be for the particular application. This would apply to both boundary lubricants and other blend components.

As has been stated above, this report describes the concept of lubricant coverage applied to the lubrication of powder blends using boundary lubricants. There are differences in the mode of action between boundary lubricants and fluid-film lubricants, and how they are affected by the blending process and changes in scale. It would be of interest to investigate whether this concept could be applied to fluid film-lubricants, and what modifications or additions to the equations presented in this report would be required.

Very often glidants, e.g., fumed silica at 0.05 – 0.1%, are also added to tablet and capsule formulations. Since it is likely that the fumed silica would also tend to be adsorbed onto the other blend particles, the surface area of the blend, either calculated or determined experimentally, should not include the contribution from the glidant. Indeed the LC concept could also be adapted to determine the optimum glidant coverage (GC) and used to facilitate development and scale-up changes in a similar manner to the boundary lubricants proposed in this report.

CONCLUSIONS

A more logical method to determine the level of boundary lubricant required for a particular tablet or powder-filled capsule formulation or formulation variant is presented using the concept of lubricant coverage (LC) based on the surface area of the blend to be compressed or encapsulated, as opposed to the traditional fixed percent incorporation that has been commonly used in pharmaceutical formulation.

With experience, the LC concept could be used to determine the likely optimum lubricant level from the initiation of a tablet or powder-filled capsule formulation development project.

The LC concept should simplify the DoE for a pharmaceutical QbD formulation design, development and scale-up project, since it would be anticipated that the required LC should not change during scale-up, and thus it would remove one potential variable from the DoE. However, it would be necessary to show that the LC was still appropriate on scale-up.

In addition, the LC concept should also aid in the investigation of excipient variability since it would allow for the easier investigation of the effects of excipient particle size such as would be encountered during the investigation of bracketing grades and blends of grades by removing the complication of the effect of lubricant level when the surface area of the particular formulation component changes due to e.g., a change in the grade of an excipient.

The LC concept can also be applied in the evaluation of alternate sourcing for pharmaceutical excipients. In addition, it could be adapted for use with glidants. The LC concept may also be used with experimentally determined values for external (envelope) surface area.

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APPENDIX A: LUBRICANT COVERAGE FOR SPHERICAL LUBRICANT PARTICLES

For a lubricant consisting of spherical particles, the number of particles in a given weight M_{lub} is, assuming that the particles are on the granule or blend particle surface:

$$n_{lub} = \frac{M_{lub}}{\frac{4}{3}\pi \frac{d_{lub}^3}{8} \cdot \rho_{lub}} \qquad \text{Eq. A1}$$

For a granule consisting of approximately spherical particles and having a weight of M_{blend}, then the number of particles is given by Equation 18. Substituting equations A1 and 18 into equation 9, cancelling through and rearranging, we get:

$$LC = \frac{M_{lub}}{4\ .\ d_{lub\ .}\ \rho_{lub}} = \frac{d_{blend}\ \cdot \rho_{blend}}{M_{blend}} \qquad \text{Eq. A2}$$

If we know the lubricant coverage we want to achieve, and assuming that all lubricant particles are adsorbed on the surface of the granulation/blend particles, we can calculate the quantity of lubricant to incorporate in a new blend or granulation according to:

$$\frac{M_{lub1}}{4\ .\ d_{lub1} \cdot \rho_{lub1}} . \frac{d_{blend1} \cdot \rho_{blend1}}{M_{blend1}} = \frac{M_{lub2}}{4\ .\ d_{lub2} \cdot \rho_{lub2}} . \frac{d_{blend2} \cdot \rho_{blend2}}{M_{blend2}} \qquad \text{Eq. A3}$$

APPENDIX B: LUBRICANT COVERAGE FOR CIRCULAR, DISC-SHAPED LUBRICANT PARTICLES

For a lubricant consisting of circular, disc-shaped particles, the number of particles in a given weight M_{lub} is, assuming that the particles are lying flat on the granule or blend particle surface:

$$n_{lub} = \frac{M_{lub}}{\pi \frac{d_{lub}^2}{4} . l_{lub.\rho lub}} \qquad \text{Eq. B1}$$

And for a granule consisting of approximately spherical particles and having a weight of M_{blend}, then the number of particles is given by Equation 18, Substituting equations B1 and 18 into equation 9, and cancelling through and rearranging, we get:

$$LC = \frac{M_{lub}}{l_{lub\ .}\ \rho_{lub}} . \frac{d_{blend}\ \cdot \rho_{blend}}{6. M_{blend}} \qquad \text{Eq. B2}$$

Then, if we know the lubricant coverage we want to achieve, and assuming that all lubricant particles are adsorbed flat on the surface of the granulation/blend particles, we can calculate the quantity of lubricant to incorporate in a new blend or granulation according to:

$$\frac{M_{lub1}}{l_{lub1} \cdot \rho_{lub1}} . \frac{d_{blend1} \cdot \rho_{blend1}}{6. M_{blend1}} = LC = \frac{M_{lub2} \cdot}{l_{lub2} \cdot \rho_{lub2}} . \frac{d_{blend2} \cdot \rho_{blend2}}{6. M_{blend2}} \qquad \text{Eq. B3}$$