Optimization of Pharmaceutical Formulations for Flow

Greg Mehos, Ph.D., P.E.
gmehos@uri.edu • www.mehos.net • 978-799-7311

Scientists and engineers working in the pharmaceutical industry often investigate solid dosage formulations that contain new active pharmaceutical ingredients (API). Formulators prepare powder blends that have a range of API, filler, binder, disintegrant, glidant, and lubricant levels and use various analyses to determine what combination of ingredients provide optimal properties such as weight, API content (or potency, which is the product of the two), uniformity, stability, and dissolution rate.

The formulator also aims to optimize the flowability of the powder blend that is to be converted into tablets. In most cases, a hopper is used to feed the powder into a tablet press. Many laboratories are equipped with a shear cell tester, which measures the cohesive strength, internal friction, compressibility, and wall friction of a powder. If these properties are measured over a range of consolidation pressures, the test results can be used to predict if and how a formulation will flow in an existing hopper, or they can be used to modify the hopper or design a new hopper that will handle the powder reliably.

Many investigators, however, attempt to define flowability by a single parameter or index. *FFC,* which is the ratio of the consolidation pressure (σ_1), to the cohesive strength (f_C) is frequently used. The ratio is often erroneously called the flow function or the flow factor. This may be partly due to the way Andrew Jenike, who pioneered powder flow property testing and bin design, defined the ratio in his classic manuscript Bulletin 123. (Jenike's Bulletin 123 can be downloaded from https://www.osti.gov/biblio/5240257.) In Bulletin 123, Jenike presented a table of *FF* values that could be used as a general classification of flowability.

Table 1
Interpretation of *FF* Values

FF	Flowability
<2	Very Cohesive
2-4	Cohesive
4-10	Easy-Flowing
>10	Free-Flowing

In Bulletin 123, Jenike defined *FF* as the ratio of the major consolidation stress to the unconfined yield strength, or in other words, the ratio of the consolidation pressure to the cohesive strength. Much later on in Bulletin 123, he also defined *FF* as the flow function, the *relationship* between the material's strength (f_C) and the major consolidation pressure σ_1, not the ratio. *FF* can therefore be either the ratio of the major consolidation pressure to the cohesive strength or the flow function, which is the relationship between the major consolidation pressure and the cohesive strength. Jenike also defined the flow factor *ff* as the ratio of the major consolidation stress σ_1 to the stresses on the abutments of a potential arch $\bar{\sigma}_1$ of powder at the hopper outlet. The flow factor can be used to calculate the size of a hopper outlet required to prevent arching.

FFC should never be called the Flow Function or the flow factor. *FFC* is equal to σ_1/f_C, the ratio of the major consolidation stress to the cohesive strength. It is best to refer to *FFC* as the flowability coefficient.

Formulators often use *FFC* as a metric for flowability, with blends having high *FFC* values deemed to be optimal. Relying on the flowability coefficient to determine if a blend has suitable flow behavior is risky, however, because: (1) *FFC* does not account for a powder's bulk density, (2) wall friction, which determines the likelihood of preferential flow and rathole formation, is ignored, and (3) *FFC* is frequently evaluated at high consolidation pressures, whereas the solids stress at the outlet of an optimally designed hopper is generally low.

As an example, the flowability of two formulations, Blend A and Blend B, are compared. Shear cell test results of the two blends are shown in Figure 1.

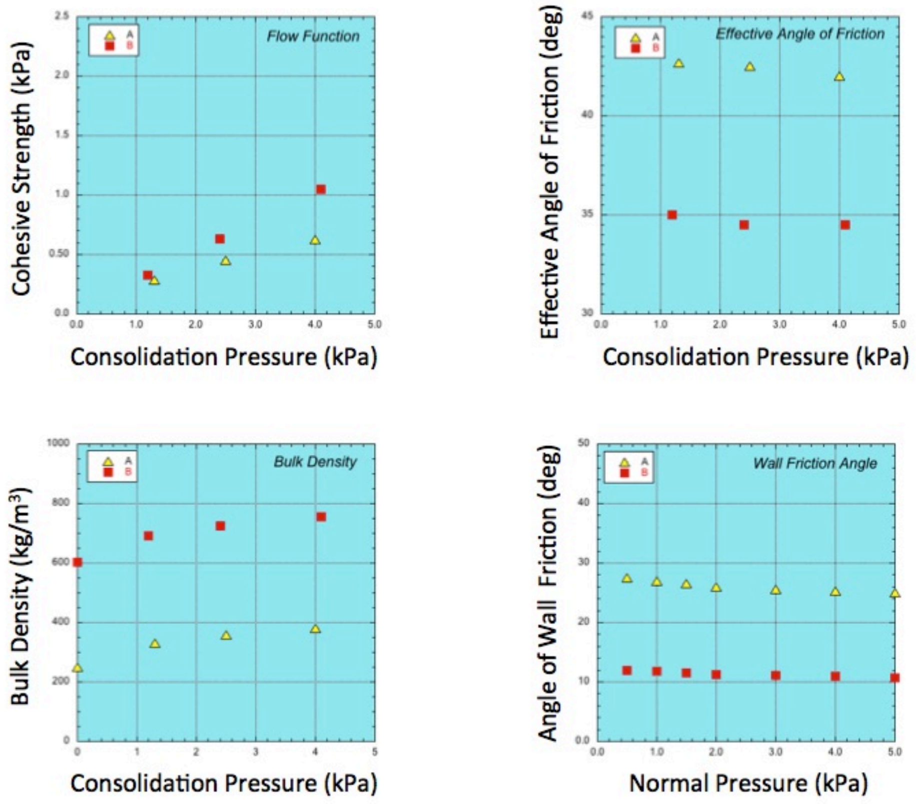

Figure 1. Shear cell test results.

From the cohesive strength test results, *FFC* is determined by dividing the consolidation pressure by the cohesive strength. *FFC* values are tabulated in Table 2.

Table 2
Tabulation of *FFC* Values

Blend	σ_1 (kPa)	f_c (kPa)	*FFC*
A	1.3	0.29	4.5
	2.5	0.45	5.6
	4.0	0.63	6.4
B	1.2	0.33	3.6
	2.4	0.63	3.8
	4.1	1.05	3.9

Comparison of the *FFC* values suggests that Blend A is superior to Blend B as its *FFC* values are greater. According to Table 1, Blend A is "easy-flowing" whereas Blend B is "cohesive".

Because the strength, internal friction, wall friction, and compressibility of each blend were measured over a range of consolidation pressures, Jenike's hopper design method given in Bulletin 123 can be used to determine the minimum outlet diameter of a hopper required to prevent arching over the outlet of a conical hopper and the recommended hopper angle to prevent ratholing. Results of the analyses are summarized in Table 3.

Table 3
Critical Hopper Outlet Diameters and Recommended Hopper Angles

Blend	Critical Arching Diameter	Recommended Mass Flow Hopper Angle (from Vertical)
A	120 mm	13°
B	23 mm	36°

The analysis is revealing. Blend A requires a larger outlet (120 mm *vs.* 23 mm for Blend B) and a much steeper hopper (13° from vertical *vs.* 36° for Blend B). Although Blend B's lower *FFC* values suggest that it has poorer flowability compared to Blend A, a proper analysis of the shear cell test results shows the opposite. Compared to Blend A, Blend B can be handled in hopper with small outlets and less shallow hopper walls.

By conducting shear cell tests over a range of consolidation pressures and performing Jenike's analysis on the test results, a formulator can optimize a powder blend for flow and have confidence that it will flow reliably. Relying on a single coefficient to assess the flowability of a formulation can be risky.