Benefits of a laser-based system to measure the solid fraction of compacted ribbons and tablets

Terry Chriss
Solid Fraction Measurement Systems

Using a laser-based method to measure the solid fraction (SF) of compacted ribbons and tablets is faster than traditional methods and the results it provides are very reproducible and operator-independent. The method makes formulating pharmaceuticals easier and simplifies the transfer of products to new equipment.

Scientists who formulate tablets generally agree that the SF (or porosity) of a roller-compacted ribbon has an important influence on the flowability of the powder produced from granulating the ribbon. Knowing the SF is also key to achieving acceptable "re-compactability" once the granulation reaches the tablet press. A review paper by Hancock et al. [1] discusses the benefits of monitoring the SF of roller-compacted ribbons and tablets when designing, optimizing, and scaling up a process to manufacture solid dosage forms.

Traditional methods of measuring the SF/porosity of ribbons and tablets include direct measurement, fluid displacement, and fluid intrusion. These techniques have been described by Hancock and Allesø et al. [2]. Most traditional techniques of measuring the SF of roller-compacted ribbons are fairly slow, requiring 30 minutes or more, which limits the utility of the measurements. With a laser-based system, it is possible to take reliable, unattended measurements in approximately 2 minutes. As a result, formulators and others can make more routine use of SF data to address production and formulation challenges.

A laser-based SF measurement system

Terminology

Because some scientists prefer to think in terms of porosity rather than SF, it's important to define each and how the two parameters relate to one another and to envelope density. SF is the fraction of a ribbon or tablet that is solid material (as opposed to pore space). Porosity, which is inversely related to SF, is the percentage of the ribbon or tablet that is pore space. The relationship between SF and porosity is expressed in Equation 1:

$$\text{SF} = 1 - \left(\frac{\text{Porosity}}{100}\right) \tag{1}$$

Equation 2 provides a means to calculate the envelope density, which refers to ratio of the mass of the ribbon or tablet to its volume:

$$\text{Envelope density} = \frac{\text{(Total mass)}}{\text{(Total volume of ribbon or tablet)}} \tag{2}$$

The basics of laser-based SF measurement

If you know the pore-free density (sometimes called the true density) of a powder before you compact it into a ribbon or tablet, determining the SF only requires measuring the envelope density (or bulk density) of the ribbon or tablet.

A laser-based SF system measures the envelope density by incorporating laser distance sensors to determine the volume of the compact. The compact is then transferred to a built-in balance to measure its mass. The ratio of the envelope density to the pore-free density (typically determined by a pycnometer) yields the SF of the compact.

$$SF = \frac{\text{Envelope density}}{\text{Pore-free density}} \quad (3)$$

How laser-based SF measurement works

To determine the envelope volume, two laser distance sensors whose beams face each other measure the distance to the lower and upper surfaces of the compact. Because the fixed distance between the two lasers is known, the thickness at the point (x,y) on the ribbon or tablet where the beams would intersect can be calculated using Equation 4:

$$T_{(x,y)} = D - U_{(x,y)} - L_{(x,y)} \quad (4)$$

where

T(x,y) is the thickness of the compact at point x,y,

D is the distance between the two lasers,

U(x,y) is the distance from the upper laser to the upper surface of the compact at x,y, and

L(x,y) is the distance from the lower laser to the lower surface of the compact at x,y.

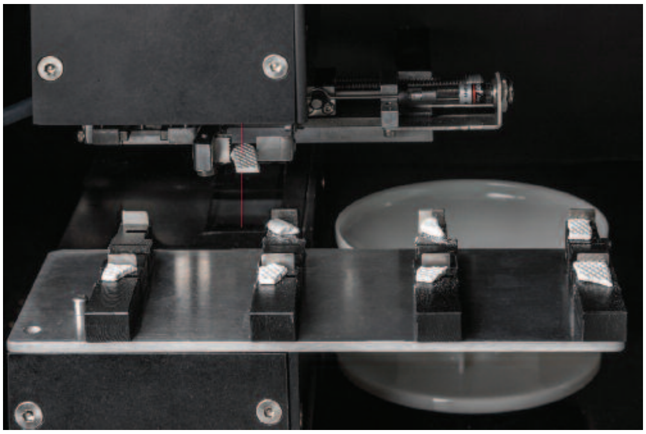
By moving the ribbon between the stationary lasers in a scanning pattern, thickness data are acquired at many (x,y) positions and the data are used to calculate the envelope volume. Knowing that value and the compact's mass enables you to calculate the SF. Working under computer control, a laser-based SF measurement system can perform a series of scans in the x direction, with the y distance between each scan selected by the user. A typical y value is 700 microns, while the typical x distance between data points is approximately 10 microns. The measurement takes approximately 2 minutes.

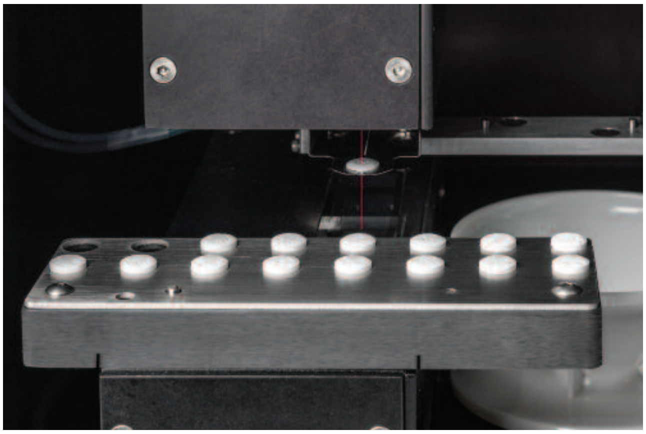
Iyer et al. [3,4] describe an early, noncommercial version of a laser-based system. Allesø, who used an early commercial version, reports excellent agreement between laser-based measurements and those obtained by the oil-intrusion method when making "back-to-back" measurements on the same samples. Unlike the oil-intrusion method, however, the laser-based approach is fast and nondestructive. The most recent commercial version of the laser-based system has an option that allows multiple ribbons or multiple tablets to be pre-loaded so you can take unattended measurements of multiple samples.

The advantages of using laser distance sensors to measure the volume of compacts include the ability to assess fragile and relatively small ribbon fragments, no special sample preparation, minimal operator training, and results that are independent of both operator experience and the specific instrument taking the measurement.

Applying SF measurement to production challenges

Determining roller compactor settings for different production rates. Once the optimal SF of a formulation is determined—one that provides adequate flowability and





An SF measurement system uses two opposed laser beams (simulated for illustration) to scan a compacted ribbon and a tablet. In the foreground are multiple ribbon pedestals and multiple tablet "nests" that allow unattended measurement.

suitable re-compactability—it is important that it be maintained. That requires correctly setting the roller compactor's force, roller gap, roll speed, etc. for the initial production requirements, and then adjusting those parameters as needed as production is scaled up. Unfortunately, knowing what force is required to produce ribbons of a certain SF at one roller gap doesn't enable you to predict the force required to produce the same SF at the new (wider) gap required to accommodate a production increase. But taking SF measurements using a laser is fast, so you can address this problem by iteratively adjusting the roller compactor's settings after changing the roller gap until the thicker compacts have the same SF as the original ribbons.

Adjusting settings when changing roller compactor models. When a formulation is developed at one facility and produced at another, the make and/or model of the equipment will likely differ. The challenge is to quickly determine the compactor settings that will preserve the SF as formulated.

Although Allesø showed that it is possible to use the same settings on two models of a single manufacturer's roller compactors and obtain the same SF, that may not always be the case. Thus, when production is moved to a different roller compactor, it can require substantial effort to determine what settings on the new compactor will yield the same SF. This is because the traditional techniques of measuring SF may be operator-dependent and thus inconsistent from one operator to another. If so, that makes facility-to-facility comparisons of SF measurements difficult. Laser-based SF measurements are not operator-dependent and are very reproducible.

Table 1 summarizes the results of an informal reproducibility study. To conduct the study, four batches of ribbons were measured in our US laboratory, then measured by multiple, newly trained operators in Denmark, and finally measured using a different instrument in the USA. The results are nearly identical [5]. These data suggest that the laser-based technique can facilitate inter-facility comparisons of the SFs of pharmaceutical compacts, including those formulated at one facility and produced at another.

The SF/porosity of tablets is one of the most important factors governing their disintegration and dissolution rates.

Likewise, if production must shift from an old roller compactor to a new one, the settings will likely need to be changed to ensure that ribbons for each affected product will have the same SF as those produced on the old model. A laser-based measurement system can minimize the time and effort required to make that type of transition.

Changing roller compactor units within the same model. It's been said that, with some compactor brands, changing compactor units—even within the same compactor model—sometimes requires adjusting the settings to achieve the same SF. Here, too, laser-based SF measurement can reduce the time, risk, and effort associated with that change.

Other applications

Routine monitoring. Because the laser-based technique is quick and doesn't use consumables, it is suitable for routine at-line (or near at-line) monitoring of SF. It can check whether machine-related issues have caused the SF to drift or whether the SF has been affected by unanticipated changes in the formulation's excipients. Because laser-based measurements are fast and can be performed on multiple preloaded ribbon samples, the operator can step away to perform other activities. Furthermore, one central system could potentially serve several production lines.

Compaction simulation. When a formulation study involves a very expensive API, scientists seek to conserve API and will often use a compactor simulator instead of a roller compactor for the initial work. Compaction simulators estimate the force and other settings required to create a ribbon that will—after granulation—achieve the desired flowability and re-compactability. This typically involves making tablet-like compacts using knurled rollers or rollers with special surface characteristics. By providing rapid feedback about the SF of these compacts,

TABLE 1

Reliability and reproducibility of SF ribbon measurements [5]

Batch ID	Date	Country	Location	Status	Number of ribbons	SF average	SF range	Standard deviation
1A	12/14	USA	Vendor facility	Acceptance testing	4	0.628	0.006	0.002
1A	3/15	Denmark	Customer facility	Operator training	7	0.633	0.007	0.003
1A	4/15	USA	Vendor facility	Testing new instrument	9	0.633	0.011	0.004
2A	12/14	USA	Vendor facility	Acceptance testing	4	0.744	0.008	0.003
2A	3/15	Denmark		Operator training	3	0.751	0.002	0.001
2A	4/15	USA	Vendor facility	Testing new instrument	7	0.752	0.008	0.003
3A	12/1	USA	Vendor facility	Acceptance testing	3	0.565	0.012	0.006
3A	3/15	Denmark		Operator training	6	0.574	0.012	0.005
3A	4/15	USA	Vendor facility	Testing new instrument	9	0.582	0.012	0.004
4A	12/1	USA	Vendor facility	Acceptance testing	3	0.684	0.009	0.005
4A	3/15	Denmark		Operator training	3	0.674	0.002	0.001
4A	4/15	USA	Vendor facility	Testing new instrument	9	0.671	0.008	0.002

a laser-based measurement system can help with this formulation work.

Tablet research. The SF/porosity of tablets is one of the most important factors governing the disintegration and dissolution rates of tablets. Few researchers use tablet SF data, however, because of the time and effort that routine SF measurements using traditional methods require. A laser-based system that takes multiple, unattended measurements can increase efficiency and make SF measurements of tablets more routine.

An in-house study demonstrated the reproducibility of tablet measurements. The study used 16 generic aspirin tablets, each of which was manually loaded 16 times into a 16-position "nest," and a total of 16 unattended "measurement runs" were made. The results indicate that, for the 16 measurements of each tablet, the standard deviation of the SF did not exceed 0.004 on any tablet, and the average standard deviation was 0.0024. By demonstrating its ability to make unattended, very repeatable, high-resolution tablet SF measurements, a laser-based system appears well suited to improving tablet research and to doing so more quickly than traditional techniques. *T&C*

References

1. Hancock, B.C., Colvin, J.T., Mullarney, M.P., and Zinchuk, A.V. The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets. Pharmaceutical Technology, 63-80, April 2003.

2. Allesø, M., Holm, R., and Holm, P., Roller compaction scale-up using roll width as scale factor and laser-based determined ribbon porosity as critical material attribute. Eur J Pharm Sci 87, 69-78, 2016.

3. Iyer, R.M., Hegde, S., Singhal, D., and Malick. W. A novel approach to determine solid fraction using a laser-based direct volume measurement device. Pharm Dev Technol 19(5), 577-582, 2014.

4. Iyer, R.M., Hegde, S., DiNuzio, J., Singhal, D., and Malick. W. The impact of roller compaction and tablet compression on physicomechanical properties of pharmaceutical excipients. Pharm Dev Technol 19(5), 583-592, 2014.

5. The complete dataset is available at www.solidfraction.com.

Terry Chriss, PhD, is president of Solid Fraction Measurement Systems, 90 Main Street, Unit 108B, Centerbrook, CT 06409. Tel. 888 770 7498, ext. 521. Website: www.solidfraction.com.