Tablet-Sticking Solutions

Screening methods and predictive models address tenacious tablet-sticking problems.

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Tablet sticking, in which material adheres to the surface of a tablet-punch face, is an ongoing and costly problem in pharmaceutical manufacturing and is a significant issue for drug-product formulators. Analytical methods can be used to troubleshoot sticking problems and develop screening methods. Experts are also seeking to increase fundamental understanding of the underlying causes of sticking and to develop predictive models to more quickly find solutions to specific sticking problems.

Many variables affect tablet sticking, including formulation (e.g., API, excipient and other components), granulation properties (e.g., particle-size distribution), tablet design (e.g., tablet shape), tablet-press conditions, tablet-tool properties and tool maintenance. There are nearly as many possible solutions as there are variables.

Tooling solutions

Tooling-equipment suppliers have found that proper tooling and tooling maintenance can help prevent sticking to a certain extent. I Holland champions a rigorous seven-step maintenance method that includes cleaning, assessing for damage or wear, repairing, measuring to ensure that dimensions are maintained, polishing, lubricating and storing properly (1).

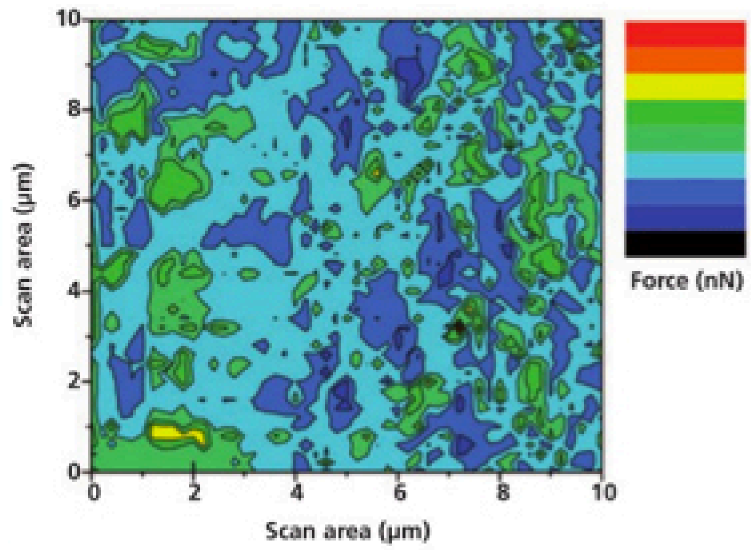
Microscopy can be used to assess the surface of a punch. "You can't see a 10-μ scratch with the naked eye, but 2-μ particles will stick to it. Suddenly, you have a film spot that acquires more powder and is then big enough to cause defects," explains Charles Kettler, director at Natoli, a tooling and equipment manufacturer. "Microscopy allows you to see if the tool has a fundamental problem." This type of analysis could be used to identify a problem with tool handling, such as whether a polishing technique is more aggressive than it should be.

Equipment suppliers have also developed special steel types and coatings to prevent sticking. Finding the best material, however, can be a time-consuming process that involves field testing at a customer's site and laboratory testing to identify a solution to each unique problem. I Holland's Tableting Science Anti-Stick Research (TSAR) program, in collaboration with the University of Nottingham's School of Pharmacy and experts from the Laboratory of Biophysics and Surface Analysis, both in the UK, is developing a predictive tool to identify the best punch or die-coating solution to prevent sticking in a given formulation. The company says that the tool will provide quick guidance without time-consuming tests (2).

TSAR-program researchers used atomic force microscopy (AFM) to map the adhesive forces on a tablet-punch face, such as the example shown in **Figure 1**. AFM can elucidate local chemical and mechanical properties, such as adhesion and elasticity, and even molecular bond rupture strength, explains Rob Blanchard, research, development and quality

Illustration by Dan Ward

Figure 1: An adhesion map shows different adhesive forces on a tablet-punch face.



systems manager at I Holland. Such adhesion maps show differences in adhesion caused by surface topography differences with various coatings at different humidities.

The TSAR researchers also used X-ray photoelectron spectroscopy (XPS), Raman spectroscopy and time-of-flight secondary ion mass spectrometry (TOF-SIMS) to visualise the chemical distribution of selected ions on the surface and better understand the interactions involved in sticking. Principle component analysis (PCA), a multivariate statistical technique, is being used to analyse these data and generate correlations to explain how the chemistry of a system affects adhesion with different surface coatings. This understanding of how the formulation components behave and interact to cause sticking will then be used to develop the predictive tool. The predictive tool will be validated using results from compression experiments with various formulations and punch-tip coatings.

Although proper maintenance and optimised coatings are essential, the root cause of sticking is often the formulation properties or particle size. If these properties are already set, manufacturers must find a solution in the tablet press or tooling. Ideally, however, the drug could be formulated to have a lower tendency for sticking.

Screening tools

Various methods are available for assessing sticking problems and screening for sticking propensity, but the use of these tools has been limited by their complexity. Many instead rely on subjective visual inspection, which limits the ability to screen consistently. To address this deficit, researchers at Pfizer developed a simple, quantitative screening tool for drug-product tablet-sticking propensity that can be used to rank the degree of sticking for many formulations and their ingredients using a custom tableting punch with a tip that can be removed to measure the amount of adhered powder (3). "This gravimetric method has been successful for classifying sticking severity during drug product design and has significantly reduced risk during scale up," says Matthew Mullarney, principal scientist at Pfizer. "We can customise both our API and drug-product formulations to ensure they do not exceed in-house threshold values in the laboratory before manufacturing any bulk-tablet supplies." The screening method can also be used to plan for manufacturing campaigns (e.g., tooling/tablet inspection frequency or cleaning requirements) and to troubleshoot the root cause of sticking problems in large-scale manufacturing.

Equipment supplier Natoli finds this gravimetric method useful for predicting the sticking tendency of formulations at or prior to clinical-scale production and has tested small amounts of API with a given formulation, tablet design, tool steel and coating for propensity to sticking (2). Further work using this method will be performed by researchers at the Natoli Institute of Industrial Pharmacy Development and Research in partnership with Long Island University's Arnold and Marie Schwartz College of Pharmacy in New York. Laboratory facilities for the institute are currently being constructed at the university and are expected to open in late 2013 with fully qualified equipment, reports Kettler. Various projects at the institute will be used to further develop fundamental understanding of tableting problems and formulation studies.

"Now that simpler tools are available for screening and classifying, both pharmaceutical companies and academic groups can focus on relating other material properties, such as molecular structure, particle size and mechanical properties, to sticking and building models that describe the sticking mechanism," adds Mullarney. "We may soon find that sticking is multimechanistic and a variety of molecular chemistry, particle and bulk-powder characterisation tools and models will be needed to parameterise the sticking mechanisms of different powders." Once these mechanisms

Figure 1 is courtesy of I Holland.

are understood, APIs and drug products can be designed to reduce sticking propensity. Current work at Pfizer is focused on understanding why some APIs appear stickier than others and investigating the contribution of a solid API's molecular attributes (e.g., surface chemistry and morphology) to sticking. "Both computational models and experimental approaches will be necessary to get us closer to the root causes. Additionally, tooling designs and surface treatments are also being studied," notes Mullarney.

Model predicts tablet microstructure

Work on building models to describe sticking is progressing. Marcial Gonzalez and Alberto Cuitino at the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) at Rutgers, the State University of New Jersey, have developed mechano-chemical models and computational methods that predict the evolution of microstructure and interparticle forces during powder compaction. Because most properties of a compacted tablet can be attributed to its microstructure, the models can be used as tools to understand and predict how manufacturing process variables affect product performance.

The tendency of powders for sticking and picking is described by the adhesion of powder to die walls and tool surfaces and can be explained by a competition mechanism between interparticle bonding and particle–wall adhesion, explained Cuitino (2). If particle–wall adhesion is stronger than interparticle bonding, the weaker interparticle bonds will break when the tablet is ejected and cause sticking or picking. If particle–wall adhesion is weaker than most interparticle bonds, internal cracks might occur. Ideally, if enough bond strength was developed during compaction, no defects will occur. If the network of particle–particle and particle–wall forces are known, competing effects can be quantified, said Cuitino. Because this measurement is not possible with current experimental techniques, the researchers developed a nonlocal formulation of contact mechanics that more accurately describes the powder system (4). This fully discrete model is based on particle mechanics and describes every particle in the powder bed as an individual entity. "The collective rearrangement and deformation of the powder bed is resolved by the fully discrete model and the microstructure of a compacted specimen is then predicted," explains Gonzalez.

External lubrication: A solution for tablet sticking

Equipment suppliers are seeing increased interest in using external lubrication to eliminate tablet sticking, address excessive ejection forces or provide an alternative to using a lubricant in the formulation if the lubricant causes problems with dissolution or hardness. In this method, a lubricant (typically magnesium stearate) is suspended in air, and using a nozzle mounted near the tablet takeoff, a fine layer of the suspension is sprayed onto the exposed upper and lower punch faces and die wall.

For some difficult products, this method can significantly reduce tablet sticking or ejection forces. Tablet geometries with a large sidewall surface area, for example, may have a high degree of friction between the tablet and the die wall. The external lubricant can be sprayed on the die wall to reduce friction and eliminate the need for excessive ejection forces, which can potentially damage equipment, says Fred Murray, president of KORSCH America, a tablet-press manufacturer.

Using external lubrication to reduce ejection force and scrape-off force helps lengthen the life of punch heads, punch faces, ejection cams and scrape-off bars used on tablet presses. It also helps reduce the amount of broken tablets, which minimises downtime and production interruptions while maximising yields, adds Michel, general manager, North America for equipment manufacturer Pharma Technology Inc. (PTI).

In some cases, external lubrication reduced ejection forces as much as 50%, and lubrication was found to improve the integrity of the outer tablet edge, adds Matt Bundenthal, direct sales manager at equipment manufacturer Fette Compacting America.

Although external lubrication does not have a dramatic effect on every product, in some, it makes a big difference, comments Bundenthal. Lubricating systems add cost and complexity, including additional cleaning requirements, notes Murray. Manufacturers may choose an alternative solution. A coating on the tooling can be used instead of external lubrication, adds Rob Blanchard, research, development and quality systems manager at I Holland. Lubricating systems will not be used for every formulation, but they are being used commercially as a solution for some problematic tablets.

External lubrication also benefits products in which a lubricant in the formulation causes problems (e.g., with dissolution or hardness). Magnesium stearate is nonsoluble in water and at concentration levels used in traditional tablet formulations (0.5% to 2%), it can create hydrophobic bridges that can delay dissolution with a significant impact on the release profile of the API(s), notes Michel. Because the external lubricant is sprayed directly where it is needed, it can be used at much lower levels (below 0.1%). External lubrication may thus be helpful for some poorly soluble APIs. External lubrication is also frequently used to produce effervescent tablets; reducing the amount of the poorly water-soluble magnesium stearate in the formulation avoids a "white film effect" upon dissolving in water, comments Nic Michel. Research by Eurand (now Aptalis) found that external lubrication could be used to improve the dissolution and disintegration rate for orally disintegrating tablets (1). In some cases, internal lubricants can degrade tablet hardness. Research done by Pfizer showed that external lubrication can significantly improve tablet hardness compared to internal lubrication over a range of compression forces (2). This research found a consistent amount of magnesium stearate across the tablet surface and throughout the tablet run.

References

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Figure 2: A fully discrete model developed by the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) at Rutgers, the State University of New Jersey, predicts a compaction curve showing the pressure applied by upper/lower punches (black line) and the pressure experienced by the die wall as a result of powder compression (blue line). The insert illustrates tablet microstructural details and interparticle and particle-wall forces (thicker lines depict larger forces). Sticking and picking tendency can be understood from these forces.

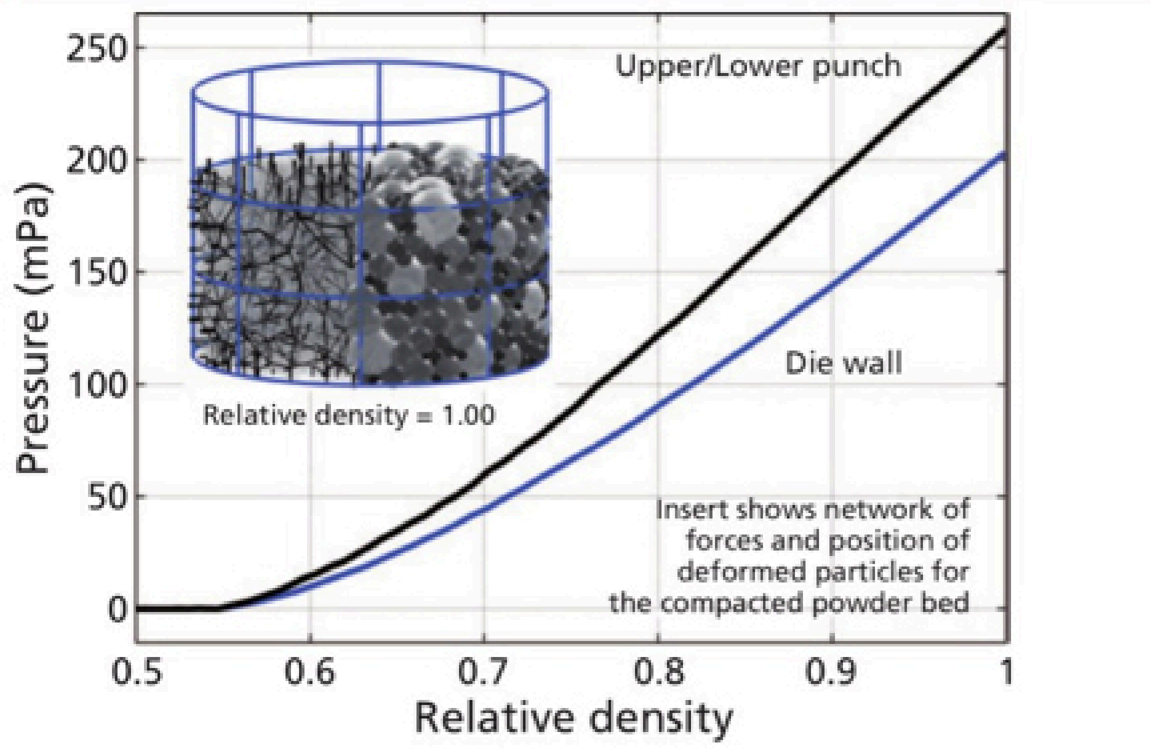

Figure 2 is courtesy of Marcial Gonzalez at the Engineering Research Center for Structured Organic Particulate Systems at Rutgers, the State University of New Jersey.

These computational models are capable of resolving and tracking the micro-structural evolution of a powder bed compacted into relative densities close to 1 (i.e., into a solid tablet with porosities close to 0, which is typical of pharmaceutical products). **Figure 2** shows a compaction curve predicted by the model; the black line corresponds to the pressure applied by upper/lower punches to achieve a given relative density, and the blue line corresponds to the pressure experienced by the die wall as a result of powder compression. The right-hand side of the insert in **Figure 2** illustrates the microstructure of the tablet with spherical particles of different sizes. In the left-hand side of the insert in **Figure 2**, lines illustrate the network of interparticle forces and particle–wall forces predicted by the model, with stronger forces indicated by thicker lines.

Experimental techniques, such as a tablet-press simulator and a tablet-hardness test, are used to calibrate material properties employed by the model (e.g., elastoplastic constants and fracture toughness of the particles). The model can be used to predict powder behaviour and properties for given tablet-press conditions (e.g., tooling geometry and punch displacement) and powder formulation (e.g., the total mass and particle-size distribution of each component of the formulation).

Other work in the early stages at C-SOPS uses tomography to measure the density gradients across the tablet at different compressions. These measurements can identify internal cracks or other near-surface defects that cannot be detected visually. These defects can be correlated to the shape of the tooling (e.g., punch shape). "Given this information, one can optimise the shape of the punch in order to minimise internal defects or avoid the formation of areas prone to chipping or capping," explains Gonzalez.

Conclusion

Current research is adding to the understanding of how adhesive forces and particle interactions cause sticking, and researchers are building models to elucidate sticking mechanisms. Results will be used to find better solutions to sticking problems by optimising tooling and, eventually, improving API and drug-product formulations.

References

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