



Valproate is a widely prescribed generic drug

## Vanishing Valproate problems one solution at a time

Valproate (valproic acid, VPA, sodium valproate, and valproate semisodium forms) are generic medications primarily used to treat epilepsy and bipolar disorder, as well as sometimes being used to prevent migraines. It was first synthesised in 1882 by Beverly S. Burton but was used in laboratories as an inert solvent for many years. It wasn't until 1962, that researcher Pierre Eymard unexpectedly discovered the anti-convulsive properties whilst using it as a vehicle for other compounds he was screening for antiseizure activity. It was approved for human use in France in 1967 and has since become the most widely prescribed antiepileptic drug worldwide. With such widespread use and its long tenure in the market, you

might think the production of Valproate tablets had been perfected, however in the solid dose industry things are never quite so simple. When aiding manufacturers in producing problematic Valproate, the most common complaint I Holland is called to help with is, of course, sticking. Sticking is one of the most common problems that a tablet manufacturer encounters, and Valproate is no different in this regard. To mass produce quality tablets, you must first resolve any sticking issues.

Sticking describes the buildup of granules on the punch-tip face, which can be caused by several factors, including the formulation's physicochemical properties and the surface characteristics of the punch face. Because sticking is such a universal problem for

tablet manufacturers, tablet tooling experts have extensively studied its causes and how to prevent it. The issue of sticking is a battle between cohesive forces holding a tablet together and adhesive forces that causes formulation to stick to the punch faces after compression. In short, if adhesion forces between the granule and the punch face are stronger than the cohesive forces in the tablet, sticking between the formulation and punch tip face occurs. To get a better understanding of these two forces, we will need an understanding of the factors affecting cohesion and adhesion.

Cohesive forces are largely affected by Van der Waals forces, capillary action, and electrostatic force. Van der Waals forces are attractive forces between molecules. They act over a short range but, in mass, combine to increase the cohesive force within a tablet and can also cause sticking. These are the primary physical forces responsible for particle-to-particle adhesion. Although these forces are very small, in mass they combine, not only increasing cohesive forces within a tablet but also creating adhesive forces (when interacting with the elements in the tools steel or coating), which can be a cause of sticking.

Capillary action can be linked to tablet formulations with high moisture content and is generated when moisture condenses in the gap between particles or between a particle and a surface to create a liquid bridge. The strength of this cohesive force can depend on the relative humidity, gap geometry, and surface chemical condition.

Capillary bridges increase the cohesive forces that help bind a tablet together. However, they can also increase the adhesion forces between the granules and the punch tip face, leading to sticking. Finally, static electricity is a major cause of sticking and often occurs when tableting dry granules. These forces can arise when tribo-charging (a transfer of electrical charges) occurs between contacting materials. The resulting force can be relatively strong and long ranged, with the potential to create both cohesive and adhesive forces.

Adhesive forces cause tablets to stick to the punch faces after compression. Adhesive force is affected by the surrounding environment, the chemistry between the formulation and the punch, the formulation's deformation mechanics, and the tooling's surface characteristics. The environment around the tableting process and even around the formulation preparation process are critical. Temperature has a huge influence on especially as some active pharmaceutical ingredients have a very low melting point. Lowering the temperature in the tableting area can help reduce sticking during compaction. Excess humidity in and around the tablet press or formulation processing equipment or in the area where the formulation is stored prior to tableting can also introduce capillary bridging between the granules and the tablet tooling, significantly increasing the chance of sticking.

The deformation mechanics, or the physical properties of the granules being compressed, can be either plastic (stays deformed) or elastic (springs back to its original shape) in nature. For formulations with more elastic, time-dependent

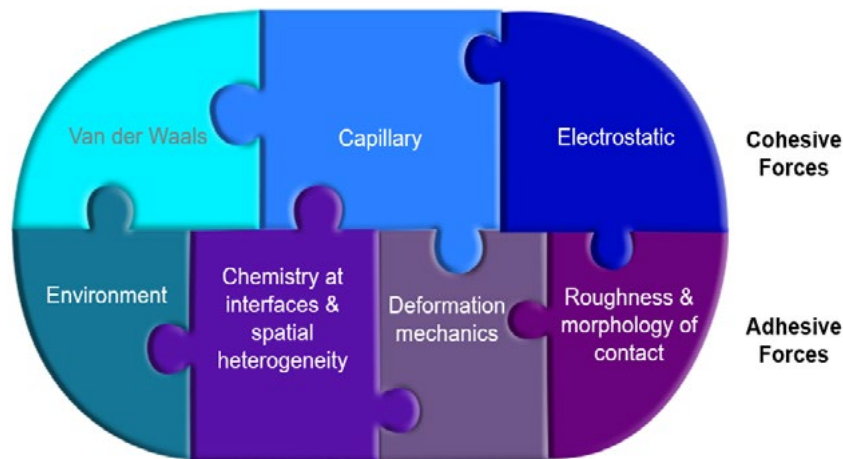


Diagram showing factors contributing to sticking

deformation behaviour, a long dwell time is critical to creating strong bonds between the particles. When a manufacturing situation requires a greater dwell time, using punches with an extended head flat will enable a suitable compression dwell time for an elastic formulation without slowing the press through sticking.

The tablet tooling surface or, morphology (surface roughness) of the punch tip face is critical to stop sticking. A common misconception is that simply polishing the punch tip faces to a mirror finish will prevent sticking. This is where I Holland can provide the solution. Coatings can be applied to tooling to imbue them with properties such as improved resistance to corrosion and wear as well as providing excellent anti-stick qualities. For sticky products like Valproate, ECExtra (E-Chrome) and CN (Chromium Nitride) are popular choices due to their extremely smooth finishes and excellent anti-stick properties.

In the past, I Holland has successfully used coatings to alleviate a customer's sticking issue when compressing Valproate. The customer contacted us and explained they were trying to produce a 500mg Valproate tablet, however, were seeing significant sticking, loss of product, and overall poor efficiency. This coupled with the tool wear being sustained during production required intervention. After investigation, which included running the formulation through our TSAR Predict model, I Holland determined that ECExtra should be applied to the tooling due to its good anti-stick qualities and its corrosion and wear-resistant properties. Also, the hydrophobic nature of the coating against the Valproate formulation, which was hygroscopic in nature (meaning it attracted water) made it a solid option. By choosing the correct coating I Holland was able to fix two issues with just one solution. Following the successful implementation of the new tooling, the customer was very pleased and can now produce high quality tablets and not

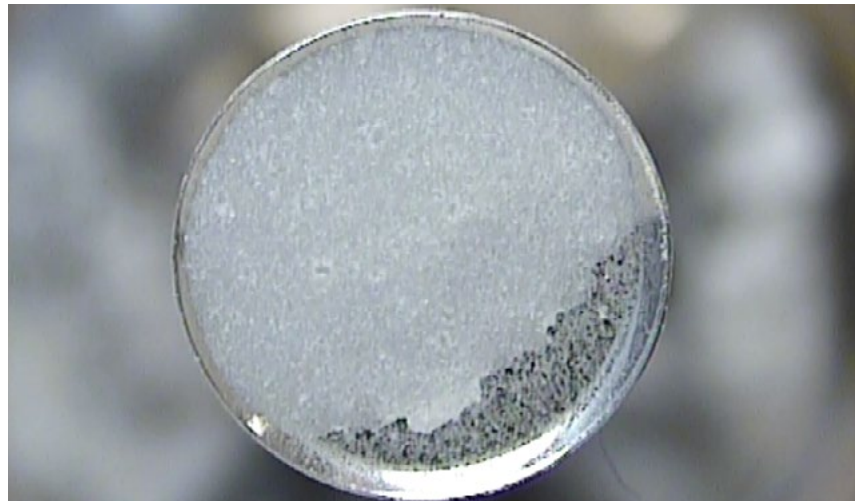
experience issues when running the press at 70-75kTPH. Whilst that is the ideal scenario, manufacturers will understand it is not often so easy to find the correct coating that compliments your formulation. After all, every tablet tells a story. Solid dose manufacturing is a case-by-case approach, and this is even more true trying to solve sticking.

TSAR~Predict was developed by I Holland, in collaboration with the University of Nottingham and experts from the Laboratory of Biophysics and Surface Analysis. It is a mathematical model that makes predictions based off thousands of trials worth of data that allow the predictive model to select the most suitable of I Holland's anti-stick punch coatings. It does this by calculating single particle adhesion to the punch tip face without time consuming and expensive field trials. To do this, the model looks at a range of parameters such as surface chemistry, temperature, humidity, size of the granule, and whether it is elastic or plastic for example. During development, the aforementioned trials were conducted using different formulations provided by an international customer base. From the tests, a database of results was built up that validated the predicted results. Along with the compression trials, substantial analysis using complex techniques such as atomic force microscopy (AFM) and time-of-flight secondary ion mass spectrometry (ToFSIMS) was undertaken. Adhesion mapping was another important element of the process. Techniques such as AFM and ToFSIMS were used to look at particles that are stuck to a punch tip and to analyse what they are chemically, thus working out what the interactions are. Any I Holland customer can contact us and use this service free of charge, all we need from you is the name of

the API or main component of the formulation. Even if this API is confidential, we can work with basic characteristic information on key physical properties.

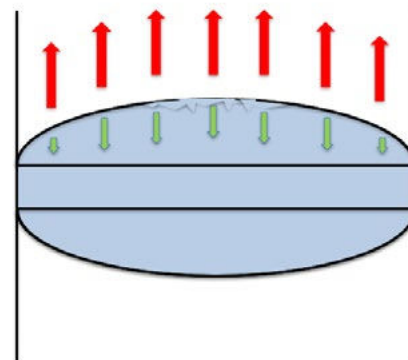
By utilizing advanced coatings and predictive tools such as TSAR Predict, manufacturers can efficiently identify solutions, reduce downtime, and maintain production quality. These innovations demonstrate the importance of combining scientific understanding with practical technology to tackle one of the most common

challenges in solid dose manufacturing. If unsure of which path to take in tackling your Valproate problems, or any other products, it is always a good idea to contact your tooling supplier, as they will most likely have experience dealing with this product. By partnering with I Holland, expert advice and tools such as TSAR Predict are never far from reach. We are always happy to provide assistance and are keen on visiting customers to take an active role in solving their problems directly.



Sticking produces tablets with weight variations

ADHESIVE FORCES > COHESIVE FORCES



The battle between adhesion and cohesion