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TABLETTING SCIENCE

Every Tablet Tells a Story

Unique tablets require unique solutions - read on!

Relieving the Pressure: Solving Losartan Issues

Patented in 1986 and approved for medical use in the United States in 1995, losartan emerged as a milestone in cardiovascular therapeutics. Developed by researchers at DuPont Merck, it was the first angiotensin II receptor blocker (ARB) to enter clinical use, offering a new option for patients who could not tolerate ACE inhibitors due to adverse effects like persistent coughs. Its approval marked a major shift in the management of hypertension, heart failure, and diabetic nephropathy.

But translating losartan's pharmacological potential into a stable, effective oral solid dosage form posed key manufacturing challenges.

Despite being chemically less complex than some legacy drugs like NSAIDs, losartan exhibits moisture sensitivity, flow variability, and requires tight control over content uniformity due to its relatively low dosage range.

Tool and coating selection, compression parameters, and coating processes must be carefully engineered to ensure consistent tablet quality and integrity, and long-term stability. As the medicine grows in popularity and demand, optimizing oral solid dose manufacturing has become essential to preserving the drug's value.

However, production isn't always smooth sailing, particularly when it comes to scaling up for high-volume output. In I Holland's experience, common challenges such as sticking and picking often significantly disrupt tablet manufacturing lines when producing losartan. These issues arise when the formulation adheres to the punch faces during compression, often due to losartan's moisture sensitivity, particle morphology, or interaction with certain excipients. This not only affects tablet appearance and weight uniformity but also leads to downtime for cleaning, increased tool wear, and ultimately reduced yield.

Addressing these challenges requires a combination of optimized punch coatings, precise environmental controls, and formulation tweaks, underscoring that even well-established drugs like losartan demand continuous attention in their oral solid dose manufacturing processes.

For example, one of I Holland's customers was producing a losartan tablet of various dosages but were observing sticking and picking on lower punches. The issues began after just a few revolutions of the press. They had experimented with different press forces and speeds but were getting the same result. The customer was very communicative with I Holland and following discussions they explained their tooling procedures, allowing a solution to be found. The customer explained:

- Sticking and picking appeared after just a few revolutions and they had the same problem at different speeds and compression forces.

- The customer had tried several ratios of precompression/ main compression, including limits with zero precompression and all precompression. There was no improvement.

- Sticking didn't always stop after cleaning with alcohol and drying the affected punches.

- There was no use of spray lubrication.

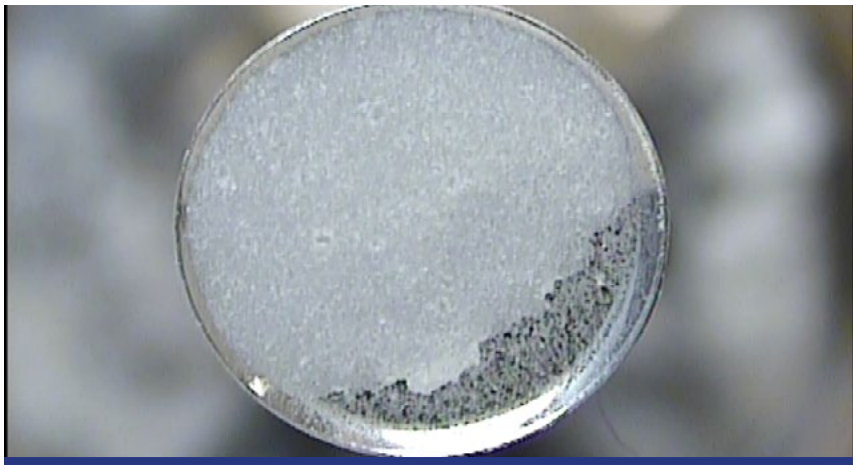
- Tools were washed with water and detergent, dried with a lint free cloth and air and then stored without oil

- They were not using an automated polishing solution

- They had experimented with removing all the API to produce placebo tablets. They found the problem went away. This gave us a good indication that the issue stemmed from the API's interaction with the tooling.

To help resolve the sticking and picking issues, I Holland first reviewed which parameters of the tablet design were registered and which could be modified. The customer then returned their tooling to I Holland, where we polished it using our MF automated polishing machine. We instructed the customer to test these polished tools directly, without any additional cleaning or handling, to eliminate external variables.

In parallel, we also manufactured a second set of tooling based on the existing design but with our CN coating, known for its anti-stick properties. The customer now had two sets to evaluate: one polished with the MF system and one CN-coated. We used TSAR~Predict (Tablet Science Anti-Stick Recommendation) with data specific to losartan, to correctly predicted that CN was the most suitable coating. TSAR is I Holland's proprietary data-driven approach that combines formulation analysis, punch surface engineering, and real-world manufacturing data to identify and recommend the most effective anti-stick solution for a given product. By referencing TSAR data, we could scientifically validate the use of CN coating as the optimal choice for mitigating the observed sticking behaviour in losartan tablet production.



A particularly bad example of sticking

The feedback from the customer was very positive: both the MF-polished tools and the CN-coated trial punches performed exceptionally well, with no signs of sticking. After 2.5 hours of continuous operation, the customer reported zero issues, confirming a significant improvement.

Given that they did not have access to an MF polishing system and were unable to invest in one at the time, they have decided to move forward with purchasing a set of upper and lower punches with CN coating. They also discussed investing in an MF polisher as automated polishing is a powerful tool for maintaining coated tooling whilst extending their lifespan. The agent has since confirmed that the customer remains satisfied, and the tooling has continued to run smoothly without any recurrence of the original problems.

As demonstrated in I Holland's customer case, these issues can severely impact efficiency, product quality, and yield. However, through a systematic approach involving detailed tooling analysis, the application of advanced surface engineering like CN anti-stick coatings, and the integration of data-driven insights from tools such as TSAR~Predict, it is possible to overcome such challenges effectively.

The successful resolution not only highlights the critical importance of ongoing innovation in oral solid dose manufacturing but also reinforces that collaboration between manufacturers and tooling experts remains essential to maintaining consistency, reliability, and scalability in pharmaceutical production.