

ORAL SOLID DOSAGE: THE TABLET

BEST PRACTICE FOR MAXIMUM TABLET QUALITY, AVOIDING THE FDA WARNING LETTER 483.

During the period 2008 through 2011, the FDA drew up 42 warning letters recalling tablets outside the specifications in terms of weight, hardness and size/thickness.

The current FDA warning letter 483 raises the question as to how it was possible for tablets outside the weight tolerance ranges to be supplied.

The reasons for the FDA reaction were assessed in an article in the "International Pharmaceutical Quality IPQ" magazine (March 2012; author: Fred Rowley). Unfortunately, there is no "single reason" why faulty tablets outside the specifications still found their way through all control stages as far as the pharmacy counter.

According to the assessment, there are two reasons why out-of-specification tablets are placed on the market:

- A) The machine operator
- B) The tablet press

This White Paper aims to help to understand the causes. It focuses on answers to problems which can be avoided by means of good operator guidance and the technologies used in tablet machinery.

To name a few examples:

Even the best machine will fail if the operator does not regularly calibrate his scales in the external test station (one reason indicated in the assessment).
Even the best machine will fail if the operator sets the cycle rates higher than the SOP guidelines in order to increase tablet output (in the author's experience).

This White Paper also aims at supporting the tablet manufacturer in finding a fault-free tablet in the tablet press' GOOD outlet channel where the recommendations outlined below are followed.

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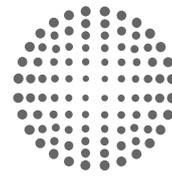
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SUMMARY



THE INFLUENCE OF THE OPERATOR

Principles and concept of tablet production

Machine operators and those responsible for the production processes have a good understanding of the manufacturing process and its tablet presses. The article by Fred Rowley nevertheless indicates some serious misunderstandings on the part of the operator.

Like many other machines deployed in OSD production, tablet presses are complex machines featuring a variety of parameters, some of which are of particular relevance, e.g. for the tablet weight.

Modern machines include technologies and constructive elements which prevent heavier or lighter tablets from reaching the Good-channel. An operator who understands the machine (and therefore the process) is generally more confident in how he handles the machine – when selecting the setting parameters, for example.

Despite the availability of any basic knowledge, it is however recommendable that you offer your operators and process managers qualification in the form of certified training by the machine manufacturer. These key training sessions are regarded as further training.

Operating the tablet press

You need a driver's license to drive a car. Likewise, verifiable and certified qualification of operators is evidence of the quality of the manufacturing enterprise as well as the quality of the respective production process.

Excerpt from the GMP (Good Manufacturing Practice) 21CFR211:

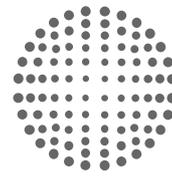
§211.25 Personnel qualification

... Each person engaged in the manufacture, processing, packing or storage of a drug product shall have education, training and experience or a combination thereof to enable that person to perform assigned functions.

Modern tablet presses are safeguarded against accidental or intentional maloperation. Password-protected parameter entries through to the 4-eye principle provide protection against unauthorized machinery settings or manipulation. All machine parameters, operating conditions, operator entries, modifications and statistics are saved in databases in line with the GMP, are tamper-proof, and can be retrieved at any time as well as being trackable/transparent.

Train your operating personnel.

Ask your machine supplier about the integrated protection features (hardware and software) and data backup (software).



THE ROLE OF THE MATERIAL TO BE PRESSED

Poor flow properties
Sticky products
Fine particles

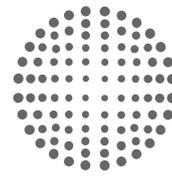
The mixing and granulation processes are followed by the product "flowing" into the tablet press. But millions of tablets are pressed by high-performance rotary presses during the production stage – and at a speed of more than six hundred thousand tablets per hour or more than 180 tablets per second. Problematic product characteristics and poor flow properties can cause considerable faults.

Experienced tablet press manufacturers have a technical laboratory or pilot plant for testing the tablet material both in laboratory and production scale. These tablet specialists avail of extensive practical knowledge covering thousands of different materials and product mixtures. They are well-versed as regards interaction by the product and the machine.

Tests in laboratory and production scale are offered through to production batches involving millions of tablets. This bodes well for subsequent major series, even before investments are made in machinery, which in turn ensures that good tablets are produced even after the validation process and the restrictions associated with it.

If the material is problematic in terms of handling, e.g. as regards its flow properties and problems relating to stickiness or compacting, the experts are able to find a solution.

Ask the machine manufacturer about the flow and press test performed on your material in his technical laboratory and pilot plant.



THE INFLUENCE OF THE TABLET PRESS

The restart phase

One critical item referred to in the article involves the machine start-up phase after changeover, cleaning or a machine stop.

Older machines only count a defined number of initial tablets before approving the good-channel.

More recent machines (see graphic) now also take consideration of other parameters: the good-channel is not approved until the press punches have returned to their final position and the compression force levels have been re-established in the set range.



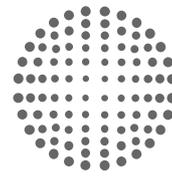
The FE55 is the first machine in the new FE series from Fette Compacting.

Ask the machine manufacturer what measures he has implemented in his machine. Ask how he minimizes the defective goods during the start-up phase and ensures that nothing runs into the good-channel. Ask about training for your operators.

The filling system

The filling system, e.g. the fill-O-matic (see graphic), plays a more or less critical role when it comes to tablet quality depending on the product (powder) and the filling hole (tablet dimensions and shape).

Modern filling systems in line with the best practice principle for correct filling and tablet weight are based on 3 adjustment and control options:



1. The turret speed and filling speed (adjusting the filling wheel speed) can be optimized for a "good" tablet.
2. Compression force monitoring checks the correct filling during the pressing process. Deviations are detected causing the (filling volume) dosage to be adjusted. Depending on the degree of deviation or frequency established, the machine establishes that the tablet is bad and ejects it and/or the machine stops.
3. Statistic tablet weight monitoring by the tablet test system supplies the tablet weight with a resolution of 1/1000 grams. The tablet weight established also leads to direct or indirect adjustment of the dosage (filling).



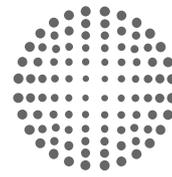
The FE55 fill-O-matic – the innovative filling unit guarantees the easy and safe supply of complex product mixtures thanks to the conical design of the filling wheel.

The dual-stage control process comprising compression force monitoring and tablet test system optimizes and guarantees filling to the target weight. Monitoring the compression force (measuring each individual tablet) and tablet weight (statistically) parameters guarantees the target weight. The evidence is guaranteed: all values measured are saved in compliance with GMP (batch recording).

The tolerance settings are always kept well within the limit values specified by the Pharmacopeia.

The measuring accuracy of the sensors used (force, weight) and the resolution of the automatic tracking (the filling volume) are much higher. As measurement of the compression force is to reliably establish the weight of the individual tablet, upper and lower compression station are equipped with load cells for the fail-safe measurement.

Ask the tablet press manufacturer about his experience and technology regarding the filling and control system using similar materials and tablet shapes to yours.



Compression force

The compression force is applied to the punches via the compression rollers (see graphic). It correlates with the tablet mass (tablet weight). By synchronizing the compression force with the tablet weight, the monitoring circuit is closed during operation.

The current state of the art involves monitoring a single tablet by measuring the force in the compression rollers. But only force measured in the power flow path supplies the requisite high measuring signal quality. The compression force curve during pressing of a single tablet is more or less flattened.

Only high spatial resolution of this force curve and establishing the peak force (using software) in these signals represents reliable transferability to the tablet weight.

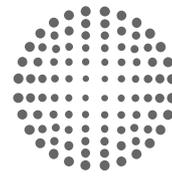
The significance and effects of force measurements for accurate tablet weights are known. This fact prompted a machine manufacturer to install the measuring sensors redundantly in the force transmission. As the pressing process involves two compression rollers (an upper and a lower compression roller), measuring sensors are integrated in both compression stations. Only when both measured values are identical are they accepted.

Deviations cause a machine reaction (individual punch fault or systematic faults) which can ultimately result in the machine coming to a stop.



Compression stations

Ask the machine manufacturer about his technology. And even when things seem to get complex in technical discussions: best technology for best tablet quality is often simple.



The tablet test system (weight, hardness, diameter and thickness)

Automatic tablet test systems such as Checkmaster (see graphic) or Autotest 4 are usually positioned beside the machine and are designed for in-process control.

Test parameters: tablet weight, tablet hardness, tablet diameter, tablet thickness and active substance analysis (NIR-Checkmaster).

At adjustable intervals, tablets are automatically fed into the external test system where they are measured in a fully-automatic process. The tablet weight and other tablet parameters measured are reported back to the tablet press via data interfaces. As already outlined in the section on the filling system, the values trigger readjustment of the machine after a variance analysis if the values are outside the specified limits (violating T1 and T2).

This closes the measuring (control) circuit and the tablet weight (and other parameters) is ensured.

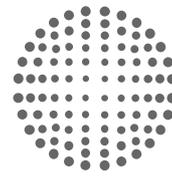


The Checkmaster tablet test device checks four of the most important tablet parameters in a fully-automatic process: weight, hardness, diameter and thickness.

Calibrating measuring equipment:

Measuring integrity for the scales used in the test system must be ensured by means of regular calibration and described in an SOP. Modern scales feature integrated test and calibration weights. Depending on fluctuations in temperature or even time, the calibration process can be performed automatically by the scales. A result protocol is generated and filed in line with GMP.

Ask your machine manufacturer about a tablet test system optimized for his machines in terms of accuracy, speed and integrability in the material flow, and ensuring data transmission or filing in accordance with GMP.



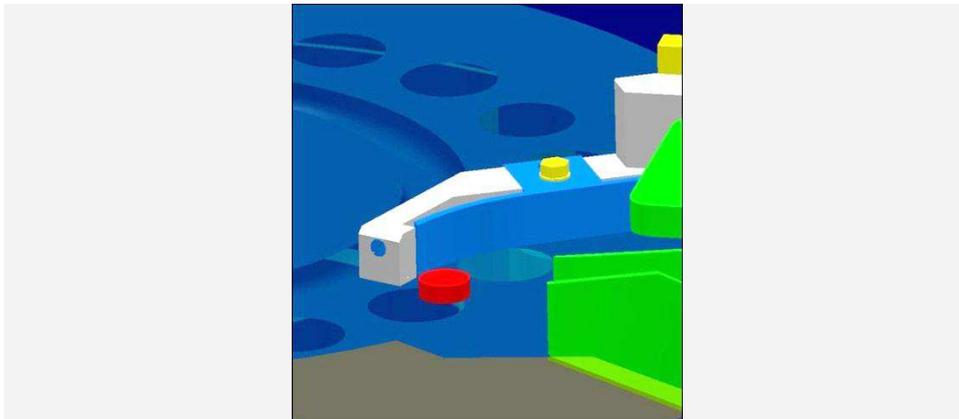
The ejection system

A tablet found to be faulty must be rejected.

While older machines still use mechanical sorting guides which are susceptible to faults as well as being slow, rejection by means of compressed air nozzles has asserted itself in newer presses (see graphic).

A clever air flow represented by air curtains in front of and inside the ejection channels ensures that the tablets are guided accordingly (into the good- and bad-channels).

The compressed air pressure in the ejector nozzle is monitored by the machine while a light barrier in the ejection channel can also monitor the correct path taken by the bad tablet in the chute.



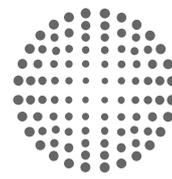
Schematic layout of the air rejection unit

Ask the manufacturer about his technology. Over the past few years, new technologies have essentially improved the safety associated with rejection and sorting systems.

Tableting tools

Tablet-specific tools (see graphic) with tablet-specific dimensions (shape and size) are required for manufacturing tablets. Tools and tableting tools and dies in particular, are certified to DIN ISO 18084 as regards dimensions, tolerances and features. There are various manufacturers on the market offering these standardized tools in various qualities.

Machine manufacturers with high demands on quality and safety have these tools in their product range.



Segment with multiple punch

The machine manufacturer is justified in pitching his ...

... **Machine competence**

Tools and machinery from a single source provide a more comprehensive guarantee as regards optimum tableting processes as well as tablet output and quality.

... **Application competence**

The optimized interplay between machines and tools guarantees top tablet quality.

... **Manufacturing competence**

The machine manufacturer knows how the tools and their materials, surface quality, polish and precision can influence optimization of total cost of ownership.

... **Innovation competence**

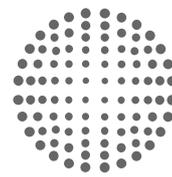
The machine manufacturer has developed special solutions for particular production problems (e.g. sticking). They guarantee a high degree of tablet quality.

And tableting tools are also subject to innovative progress: machinery used today avails of patented segment technology featuring measurable additional benefits in terms of costs and quality.

Ask the machine manufacturer about his tools. A good manufacturer includes them in his supply range. He will show you the advantages, including the outstanding benefits of new segment technology.

Software (user interface, statistics, electronic batch recording, password access)

A good software product offering comprehensible diagnoses provides operators with support via the graphic user interface (see graphic) during operation and in the event of faults. In the pharmaceutical industry, it also complies with the requirements to 21CFR Part 11.



Outlining everything in detail would exceed the scope of this paper which is why only the most important software features are listed here.

- User Management (password-protected)
- Electronic Batch Recording
- Audit Trail (change protocol)
- Diagnosis Log
- Operating information in plain text / local language
- Context-sensitive help functions available in plain text
- Data connection to MES via OPC

The author is aware of the fact that some of these abbreviations are only known to IT experts.



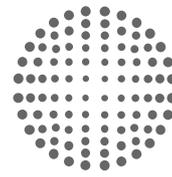
Process graphics

Ask about an easy and intuitive user interface which depicts the process and machine status. And ask about terms such as Audit Trail, Batch Recording, User Level Management and Access Authorization for operators.

Machine manufacturer expertise

The expertise availed of by a machine manufacturer can be measured on the basis of four criteria:

- | | |
|---|--|
| 1. History on the market | = knowledge and experience |
| 2. Innovative strength | = suitable technologies |
| 3. Number of pharmaceutical installations | = reputation, pharmaceutical expertise |
| 4. Contactable on site | = short paths, technical laboratory, service |



SUMMARY

The manufacturer and his technologies play an essential role in the manufacture of tablets. The innovations and technologies deployed in machinery today are milestones which have always evolved as a result of demands for improvement in tablet manufacturing.

As already mentioned at the beginning of this article, the machine operator plays a major role. Understanding the contexts and factors of relevance in the manufacture of a GOOD tablet are key prerequisites while training is essential.

A reliable machine manufacturer with many years of experience will be able to stand by his machines and provide the user with support in each of the items listed above. Such support integrates operator training as well as tests with products in the manufacturer's own technical laboratory and pilot plant where experience gleaned over many decades is focused and employees are the true experts. Talk to them!

The machine manufacturer can and will provide first-class support and pass on what he knows. He can offer advice, service, tools and training – near the user or even on his premises.

What a machine manufacturer should be capable of – at a glance:

- ✓ He has gleaned knowledge and many years of experience with tablets.
- ✓ He is in the vicinity of the user.
- ✓ He is a technology driver and offers the latest technologies and innovations.
- ✓ He offers a test laboratory / pilot plant.
- ✓ He has a wide range of services, tests and training options worldwide.
- ✓ He supplies tableting tools for his machines.
- ✓ He has a good financial background.
- ✓ He can list a large number of installations in the pharmaceutical industry.
- ✓ He is a partner to all pharmaceutical companies all over the world.
- ✓ He is a reliable partner across the entire life cycle of the machine.
- ✓ He offers measurable and sustainable advantages in terms of the total cost of ownership.