INTRODUCTION

This article is designed to facilitate the understanding of the general principles of tablet press instrumentation and the benefits thereof by the formulators, process engineers, validation specialists, and quality assurance personnel, as well as production floor supervisors who would like to understand the basic standards and techniques of getting information about their tableting process.

HISTORY OF TABLET PRESS INSTRUMENTATION

In 1952–1954 Higuchi and his group[1] have instrumented upper and lower compression, ejection, and punch displacement on an eccentric tablet press, and pioneered the modern study of compaction process. This work was followed by Nelson[2,3] who was the member of the original group.

In 1966, a U.S. patent was granted to Knoechel and co-workers[4] for force measurement on a tablet press. This patent was followed by two seminal articles in Journal of Pharmaceutical Sciences on the practical applications of instrumented rotary tablet machines.[5,6] A number of other patents related to press instrumentation and control followed from 1973 on ward.[7–15]

Despite the availability of published designs for press instrumentation, the reader is encouraged to peruse Ridgeway Watt’s[28] volume. There have been a number of papers published on various disparate instrumentation topics, and in a recent volume by Muñoz-Ruiz and Vromans,[29] there are two good articles on the subject—but, unfortunately, they deal with marginal issues of single station press and instrumented punch only.

DATA ACQUISITION PRINCIPLES: FROM TRANSDUCERS TO COMPUTERS

To monitor and control a tablet press, certain sensors must be installed at specific locations on the machine. These sensors are called transducers. In general, a transducer is a device that converts energy from one form to another (e.g., force to voltage). Tablet press transducers typically measure applied force, turret speed, or punch position. Because the signals coming from such transducers are normally in millivolts, they need to be amplified and then converted to digital form in order to be processed by a data acquisition system.

Piezoelectric Gages

Historically, high impedance piezoelectric transducers that employ quartz crystals were used in early stages of press instrumentation. When subject to stress, the crystal accumulates electrostatic charge that is directly proportional to the applied force. Both low and (more modern) high impedance piezoelectric gages have high-frequency response, but may exhibit signal drifting due to charge...
leakage (approximately 0.04% decay per second can be seen in modern piezoelectric transducers). Nowadays, the preferred way of instrumenting tablet presses is with strain gages.

**Strain Gages**

Strain gages are foil, wire, or semiconductor devices that convert pressure or force into electrical voltage. When a stress is applied to a thin wire, it becomes longer and thinner. Both factors contribute to increased electrical resistance. If an electrical current is sent through this wire, it will be affected by the changes in the resistance of the conduit. This principle is used in strain gage-based transducers. Foil gages, known for robust application range, useful nominal resistance, and reliable sensitivity control, are most commonly used for instrumentation of compression, precompression, and ejection forces. Semiconductor-based strain gages are inherently more sensitive but suffer from high electrical noise and temperature sensitivity. Such gages are not commonly used in tablet press instrumentation except for measurement of die-wall pressure and take-off forces.

**Wheatstone Bridge**

Wheatstone bridge (Fig. 1) is a special arrangement of strain gages that is used to ensure signal balancing. The “full” bridge is composed of two pairs of resistors in a circle, with two parallel branches used for input and two for signal output. By applying the so-called excitation voltage (typically, 10 V DC) to the bridge input and changing the resistance of different “legs” of the bridge by adding special resistors, we can make sure that there is a zero output voltage when no load is applied to the transducer. This is called zero balance. Once the bridge is balanced, a small perturbation in the resistance of any “leg” of the bridge results in a nonzero signal output.

The output of the Wheatstone bridge is normally expressed in millivolts per volt of excitation per unit of applied force. For example, sensitivity of 0.2 mV/V/kN means that applying, say, 10 kN force and 10 V excitation will produce 20 mV output. To utilize such output, it usually needs to be amplified several hundred times to reach units of volts.

Another important function of the bridge is balancing of temperature effects. Although individual strain gages are sensitive to temperature fluctuations, Wheatstone bridge arrangement provides for temperature sensitivity compensation, so that the resulting transducer is no longer changing its output to any significant degree when it heats up.

Because the output of these bridges is in the range of millivolts, the cables utilized to carry the signal are normally shielded with a braided or foil-lined sheath around individual wires. The shield, as a rule, is connected to the amplifier, but never touches the actual instrumented equipment (i.e., tablet press). If this rule is violated, a ground loop may generate electrical noise and present a dangerous electrical shock hazard.

**Gage Factor**

The gage factor is a specific characteristic of a strain gage. It is calculated as the change in resistance relative to unit strain that has caused this change. Strain gages that are commonly used for tablet press instrumentation are made from copper–nickel alloy and have a gage factor of about 2. In a typical bending beam application (such as compression roll transducer), one side of the beam experiences tension while the other side undergoes compression. By mounting two gages on each side, the sensitivity of the transducer can be doubled.

Strain gages have to be bonded to areas of machine parts that are most sensitive to applied force. Such areas can be identified with the use of polarized light technique that “points out” the stress distribution.

**Manufacturing a Force Transducer**

Usually, instrumentation designs are proprietary and specific detail drawings are held in fiducial capacity. Each force transducer is custom designed for a particular machine part. Overall specifications are taken from the actual party and/or manufacturer approved drawings.

Duplicate steel members, such as pins and cams, are normally made from A2 tool steel in a fully annealed
(softened) state. Original machine parts are first annealed, if required. The member is then machined, hardened to Rockwell 60–64, tested, and finally, ground to specified dimensions.

It is highly advantageous to determine stress distribution using polarized light beams identifying the areas of maximum strain yet avoiding areas of uneven strain.

A typical procedure of transducer manufacturing in a professional gaging lab might be as follows. Foil type strain gages are bonded to the steel member utilizing a high-performance 100% solid epoxy system adhesive under controlled heating rate conditions. After intrabridge wiring is completed using solid conductor wiring (to prevent electrical noise), multistrand wire cabling with a combination of foil and braided insulation is connected to the bridge. Wire anchoring is achieved utilizing epoxy adhesive and protected with a combination of latex-based adhesives and/or epoxy resins. Lead wire cabling is protected by Teflon outer shield, as well as inner braided wire shield. The Teflon to steel joint is sealed with epoxy but should not be subject to stresses that would cause the cable to kink or yield in such a way as to expose the inner braided wire shield. Protective coatings are then applied and final postcure heating is performed for at least 2 hr at a temperature approximately 50°C above the transducer normal operating temperature (approximately 175 or 105°C). A silicon-based adhesive, such as RTV, is used to fill large cavities while maintaining a low modulus of elasticity, preventing undue influence upon the actual strain measurement. The coating is resilient to moderate mechanical abrasion, as well as most solvents, oils, cleaners, etc. It is not intended for protection against penetrating sharp objects.

A high-quality connector is then attached to the cable. The next step is to perform offset zeroing with fixed, 1% precision, low-temperature coefficient resistors, followed by NIST (National Institute for Standards and Technology) traceable calibration.

It is worth noting that, in general, the duplicate members are not made of corrosion-resistant steel, because high tensile strength and ability to be easily machined are required. Prior to storage, the surface should be treated like any high-grade tablet press punch steel will be treated; a thin coating of oil should be used after wiping with alcohol.

**Load Cells**

In some cases, where appropriate, a load cell can be used in place of bonded strain gages.

A load cell is a strain gage bridge in an enclosure forming a complete transducer device.

Like any properly made transducer, it produces an output signal proportional to the applied load. Unlike custom-made transducers that require application of strain gages directly to press parts, load cells are self-contained and can be placed on a press in specially machined cavities to be easily replaced or serviced. As a drawback, load cells generally are less sensitive or less suited to measure the absolute force than custom-made strain gage transducers. Load cells can be used on punch holders in a single station press. Another example of load cell use is a die assembly for calibration of existing traducers on a press.

**Linear Variable Differential Transformer**

Linear variable differential transformer (LVDT, Fig. 2) is a device that produces voltage proportional to the position of a core rod inside a cylinder body. It measures displacement or a position of an object relative to some predefined zero location. On tablet presses, LVDTs are used to measure punch displacement and in-die thickness. They generally have very high precision and accuracy, but there are numerous practical concerns regarding improper mounting or maintenance of such transducers on tablet presses.

**Proximity Switch**

Proximity switch (Fig. 3) is a noncontact electromagnetic pickup device that senses the presence of metal. On tablet presses, it is widely used to detect the beginning of a turret
revolution, to identify stations and to facilitate peak detection in tablet force control applications.

**Instrumentation Amplifier and Signal Conditioning**

Signal conditioning involves primarily an amplifier that provides the excitation voltage, as well as gain (a factor used in converting millivolt output of the strain gage bridge to the volt-based range of the input of the data acquisition device).

Instrumentation amplifier is different from other types of amplifiers in that the signal from each side of the transducer bridge is amplified separately and then the difference between the two amplified signals is, in turn, amplified. As a result, noise from both sides of the sensors is reduced.

Some instrumentation amplifiers also offer filter functionality. A filter circuit combines resistors and capacitors that act to block the undesirable frequencies. It is a fact, however, that a good transducer should provide a clean signal. Use of analog or digital filters may cause the loss of some important portions of the signal that one is attempting to measure. Frequency filters may cause the measured compression force peak, for example, to be skewed toward the trailing edge of the peak and can yield a lower than actual peak force.

Because filters distort the signal, they must be avoided unless absolutely necessary. In many cases, better electronics may make filter use obsolete. For example, the so-called antialiasing filter that is used to condition a high-frequency signal for a slow sampling rate is generally not required for tablet press applications if modern fast speed data acquisition devices are used for signal processing.

In addition to amplification, excitation, and filtering, signal-conditioning devices may provide isolation, voltage division, surge protection, and current-to-voltage conversion.

**Instrumentation Terms: Definitions**

Several important terms may be now defined with respect to transducers and signal conditioning:

- **Full Scale (FS):** The total interval over which a transducer is intended to operate. Also, it can define the output from transducer when the maximum load is applied.
- **Excitation:** The voltage applied to the input terminals of a strain gage bridge.
- **Accuracy:** The closeness with which a measurement approaches the true value of a variable being measured. It defines the error of reading. Good tablet press transducers have at least 1% accuracy (with this level of accuracy, for example, a compression force transducer with 50 kN FS will produce at most an error of 500 N).
- **Precision:** Reproducibility of a measurement, i.e., how much successive readings of the same fixed value of a variable differ from one another. If a person is shooting darts, for example, the accuracy is determined by how close to the bull’s eye the darts have landed, while the precision will be indicated by how close the darts are to each other.
- **Resolution:** The smallest change in measured value that the instrument can detect.
- **Dynamic range of a transducer:** The difference between the maximal FS level and the lowest detectable signal. Measured in decibels (dB), it indicates the ratio of signal maximum to minimum levels:

\[
\text{dB} = 10 \log_{10} \left( \frac{S_{\text{max}}}{S_{\text{min}}} \right)
\]

Some press sensors may have a rather narrow dynamic range not necessarily correlated with accuracy. For example, a very accurate compression roll pin designed to measure 50 kN force may not detect 5 kN signal.

- **Calibration:** Comparison of transducer outputs at standard test loads to output of a known standard at the same load levels. A line representing the best fit to data is called a calibration graph.
- **Calibration factor:** A load value in engineering units that a transducer will indicate for each volt of output, after amplifier gain and balance. Calibration factor is usually expressed in relation to FS.
- **Shunt calibration:** A procedure of transducer testing when a resistor with a known value is connected to one leg of the bridge. The output should correspond to the voltage specified in the calibration certificate. If it does not, something is wrong and the transducer needs to be inspected for possible damage or recalibrated.
Tablet Press Instrumentation

- **Sensitivity**: The ratio of a change in measurement value to a change in measured variable. For example, if a person ate a 1 lb steak and the bathroom scale shows a 2 lb increase in the body weight, then the scale can be called as insensitive (ratio is far from unity).
- **Traceability**: The step-by-step transfer process by which the transducer calibration can be related to primary standards. During any calibration process, a transducer is compared to a known standard. National or international institutions usually prescribe the standards. In the United States, such governing body is the NIST.
- **Measurement errors**: Any discrepancies between the measured values and the reported results over the entire FS. Such errors include, but are not limited to:
  - **Nonlinearity**: The maximum deviation of the calibration points from a regression line (best fit to the data), expressed as a percentage of the rated FS output and measured on increasing load only.
  - **Repeatability**: The maximum difference between transducer output readings for repeated applied loads under identical loading and environmental conditions. It indicates the ability of an instrument to give identical results in successive readings.
  - **Hysteresis**: The maximum difference between transducer output readings for the same applied load. One reading is obtained by increasing the load from zero and the other reading is obtained by decreasing the load from the rated FS load. Measurements should be taken as rapidly as possible to minimize creep.
  - **Return to zero**: The difference in two readings: one, at no load, and the second one, after the FS load was applied and removed.

A good transducer is one with the combined (or maximum) error of less than 1% of the FS.

### Analog-to-Digital Converters

In order to convey analog output (in volts) from a transducer to a computer, it has to be converted into a sequence of binary digital numbers. Modern analog-to-digital converter (ADC) boards are sophisticated high-speed electronic devices that are classified by the input resolution, as well as the range of input voltages and sampling rates.

Resolution of an ADC board is measured in bits. Bit (abbreviation for binary unit) is a unit of information equal to one binary decision (such as “yes or no,” “on or off”). A 12-bit system provides a resolution of one part in \(2^{12} = 4096\), or approximately 0.025% of FS. Likewise, 16 bits correspond to one part in \(2^{16} = 65,536\), or approximately 0.0015% of FS (for tablet press applications, such resolution is usually excessive).

Thus, resolution of ADC board limits not only the dynamic range but also the overall system accuracy. Alternatively, a higher resolution may be required to retain a certain level of accuracy within a given dynamic range. For example, a 0.5% accurate transducer with 80 dB dynamic range requires at least 12-bit ADC resolution.

Amplifying a low-level signal by 10 or 100 times increases the effective resolution by more than 3 and 6 bits, respectively. On the other hand, increasing an ADC resolution cannot benefit the overall system accuracy if other components, such as amplifier or transducer, have a lower resolution.

When an input signal change is smaller than the system’s minimum resolution, then that event will go undetected. For example, for an FS of 10 V (corresponding to, say, a compression transducer output of 50 kN), using a 12-bit ADC, any signal that does not exceed 2.44 mV (12.2 N) will not be seen by the system.

The ADC boards also differ by the effective sampling rate range. Sampling rate speed is measured in Hertz (times per second). The signals coming from a tablet press have a frequency of not more that 100 Hz (compression events per second). To avoid aliasing (losing resolution of the incoming signal due to slow sampling rate), the sampling rate should be at least twice the highest frequency of the signal. Most ADC boards used for data collection in tableting applications have a sampling rate of 5–20 times larger than signal frequency. That is why antialiasing filters are not required.

### Computers and Data Acquisition Software

Overall accuracy of a data acquisition system is determined by the worst-case error of all its components. One should be aware of the fact that most system errors come neither from transducers (0.5%–1% accuracy) nor from A/D converters (0.025% accuracy) but from the software analyzing the data (round-off errors, improper sampling rate, or algorithms).

The speed and capacity of a data acquisition system depend on the computer’s processor and hard drive specifications. The real-time data from transducers is streamlined to both the screen (for monitoring) and the disk (for replay and analysis). Generally speaking, “real-time” processing means reporting any change in the phenomena under study as it happens. Interestingly, but
a high-speed data collection from a tablet press and a bookkeeping home finance program used on a monthly basis to balance the checkbook can both be related to as “real-time” software. The difference is in the time frames. For a tablet press, we are collecting data that need to be sampled and processed in milliseconds (a typical compression event may take 25 msec), while for home bookkeeping once a month will do.

Most vendors supplying transducers, signal conditioning, and computer hardware adhere to practical standards, e.g., there are some accepted norms for strain gage factors, combined errors, sensitivity, ADC resolution, and sampling rate. The difference between vendors is apparent when we compare software because there are no universally established standards of user interface. Yet the hardware is “transparent” (i.e., invisible) to the end user—day in and day out the user is facing the screen, keyboard, and mouse. The ease of software use, bug-free analysis of signals coming from transducers, reliability of statistical computations, quality of graphs and reports, and validatability of the system—all of the above contribute to the quality of the data acquisition software.

Proper validation tests of a data acquisition system should include calculation of an overall system error when the input is known and controlled (e.g., an NIST traceable signal generator providing a sinusoidal signal with a known amplitude and frequency, to simulate compression events on a press). Comparing the output (for example, peak heights as reported by the software) to the known input, the overall system error can be reliably established.

The R&D grade instrumentation, in contrast, requires placing the strain gages as close to the punch tips as possible in a vertical alignment with the direction of force application. In practice, it means placing the gages in a compression roll pin, so that the resulting measurement would reflect the absolute force. Thus, we can differentiate between the force on the upper and lower punch, and moreover, we can compare readings of the compression force from different tablet presses.

**Compression Force Measurement**

On a typical R&D grade compression transducer, a compression roll pin is machined with incisions made for placing strain gages (Fig. 4). The actual form of these cavities constitutes the very art of the transducer design that is usually proprietary and is based on the know-how of instrumentation vendor.

It hast to be noted that there could be an upper or lower instrumented compression roll pin.

The resulting measurement of a compression force is highly correlated with a variety of tablet properties. As compression increases, so does tablet hardness and weight (at constant thickness and true density), along with a force required to eject a tablet. Many variables affect the force of compression: press settings, press speed, punch length variation, punch wear, and damage, formulation and excipient properties.

**Precompression Force Measurement**

Similar to instrumented compression pin, there is a way to instrument an upper or lower instrumented precompression roll pin. Precompression, if it exists on a press, is used for de-aerating and initial tamping of the powder mass in the die and usually helps to achieve the desired hardness without capping or lamination. The force...
of precompression is normally a fraction of the compression force.

**Ejection Force Measurement**

There are many ways to instrument an ejection cam. A preferred arrangement of strain gages (the so-called “shear force” design) does not require any discontinuities in the cam surface, and, most importantly, it provides for a very good linearity of the resulting signal (Fig. 5).

Larger ejection forces may lead to an increased wear on tooling and eject cam surface. Ejection force may also be used to evaluate the effectiveness of lubrication (of both the press and the product) and punch sticking. Sensitivity and linearity of an ejection transducer are design dependent: shear force designs are always preferable over split cam or cantilevered beam designs.

**Take-Off Force Measurement**

Take-off force is monitored by mounting a strain gage to a cantilever beam on a press feed frame (in front of the take-off blade, Fig. 6). It is done to measure adhesion of tablets to lower punch face. Such adhesion is indicative of underlubricated granulation, poor tooling face design, die-wall binding, and tablet capping. [32,33]

**Speed Measurement and Station ID Determination**

Station identification and press speed are usually obtained by means of a revolution counter (proximity switch). It is installed on the press in order to mark the beginning of a turret revolution and thus enable station identification and speed calculations by system software.

In addition, a linear arrangement of proximity switches can mark the beginning and end of a compression event (information that is vital for tablet weight controllers) and also indicate missing punches.

Other points of instrumentation on a tablet press are as follows:

- A rotary press pull-up cam can be instrumented to measure the upper punch pull-up force (the force required to pull up the upper punch from the die). Likewise, the lower punch pull-down force is measured on a bolt holding the pull-down cam. [34] It is useful in determining the smoothness of press operation (extent of lubrication, cleanliness of the machine, and long batch fatigue buildup).

- Punch displacement measurements are easily done on a single station press by attaching LVDT to the punch. On a rotary press, such measurements can be done by means of slip ring, telemetry, or instrumented punch. Punch displacement profiles may be used in conjunction with compression force to estimate work of compression and work of expansion (measure of elasticity). Because capping tendency increases with the punch penetration depth, it may be desirable to monitor actual punch movement into the die. The shape of a force–displacement curve is an indication of the relative elasticity or plasticity of the material; whereas plastic deformation is desirable for stronger tablets, excess plasticity usually results in tablets that tend to cap and laminate. [35–37]

- Radial and axial die-wall force measurements also provide an insight into the compaction mechanism of the material and may indicate a die-wall binding (sticking) that is, in effect, a negative pull on lower punch. The radial die-wall pressure due to friction is material-specific and is more evenly distributed inside the die with an addition of a lubricant. [38–44] Instrumentation of the die presents a technological challenge because pressure is distributed nonlinearly.

![Fig. 5 Instrumented ejection cam.](image)

![Fig. 6 Instrumented take-off bar.](image)
with respect to tablet position inside the die and depends on tablet thickness.\cite{45,46} 
- In-die temperature can be monitored for heat-sensitive formulation, such as ibuprofen.\cite{47,48}

**Instrumented Punch**

Several vendors offer instrumented punch, i.e., a punch that has strain gages and other instrumentation built-in. The data are then accumulated or transmitted via telemetry to a stationary computer. Such devices are versatile enough to report compression forces and either punch displacement or acceleration, and, at least in theory, they can be easily moved from press to press.\cite{49,50} However, one should keep in mind that each instrumented punch is limited to one size and shape of the tooling, and is limited to one station, compared to roll pin instrumentation that reports data for all stations and any tooling. In addition, instrumented punches are either rather cumbersome to install, or else they report a useless measurement of punch acceleration instead of punch displacement. Attempts to calculate displacement from acceleration so far could not be validated.

**Single Punch Press for R&D**

Single punch eccentric presses are often used in early stages of formulation development because they do not require a large amount of powder. Another benefit is that they allow relatively inexpensive measurements of die forces and punch displacement (there is no rotation of die table and therefore no need to use expensive telemetry methods). This is the primary reason why so much basic research and product development were done on eccentric machines.\cite{51} Negative considerations are that a special tooling is required (usually, F tooling), and also that speed of compaction is too slow compared to rotary presses. As it will be seen later, the speed is a crucial factor in tableting process and therefore the results obtained on single punch presses do not directly correlate with tablets made on rotary machines.

**Benefits of Press Instrumentation**

Among many benefits of press instrumentation, formulation fingerprinting is perhaps the most obvious. Compressibility and ejection profiles, as well as dissolution and disintegration curves related to compression force, are unique for each formulation and can be used as a batch record. For process optimization, one can include compression or precompression force and speed factors in experimental design. Compressibility and ejection profiles can be used for excipient and lubricant evaluation. Other useful product development and optimization tools include response surface, Heckel, and force–thickness plots. Scientifically reliable process scale-up cannot be achieved without instrumentation data providing scale-up parameters such as dwell time, density, and energy of a tablet.

In a pilot plant and on the production floor, proper instrumentation can be used for press troubleshooting, to warn about tooling irregularities, worn-out cams, sticking punches, underlubricated dies, and so on. Finally, instrumentation is widely used for tablet weight control.

**Instrumentation for Formulation Development**

Much of the current body of knowledge about compaction properties of pharmaceutical materials came from instrumented tablet presses.\cite{52–56} Many tablet properties, such as tensile strength (hardness) and porosity can be predicted from force profiles.\cite{57–59}

Work of compaction (a scale-up parameter) can be obtained with proper instrumentation.\cite{60,61} Information about the plasticity of materials can be derived from force–time curves.\cite{62–64}

The phenomenon studied with the help of instrumentation is the so-called “lag time” (the time difference between peak of compression and maximum punch penetration). The extent of this lag is indicative of compaction mechanisms of the powder being compressed.\cite{65,66}

**Typical waveform**

Let us have a look at the actual waveforms that one may obtain from an instrumented tablet press (Fig. 7). The black proximity switch trace that marks the beginning of a revolution should be noticed. On this press, precompression and compression events coincide in time (they relate to different punches, of course). They are followed by the ejection and take-off.

**Compactibility profile**

When the average tablet hardness is plotted against the average compression peak force, we get the so-called compactibility profile that allows us to compare different formulations or different processing speeds. Referring to Fig. 8, which formulation is better? Well, formulation No. 2 makes harder tablets for the same compression force, and this would mean less wear and tear on the production press is required to achieve desired hardness. On the other
hand, if the hardness tolerance limits are exceptionally narrow, the steeper slope of formulation No. 2 may be a detriment.

Lubricant profile

A certain quantity of lubricant must be present in the granulation to reduce the friction that occurs at the die wall as the tablet is being ejected, as well as to prevent sticking of the tablet to the face of the punches. Without instrumented ejection cam and take-off bar, no objective estimate of an optimal lubricant level is possible, and the “best” formulation is usually the last one prepared.

The plot shown in Fig. 9 will help a formulator to determine the optimal amount of lubricant. Obviously, one would try to minimize the ejection force (again, to reduce wear and tear on the ejection cam of the production press), and yet to avoid the pitfalls of having too much lubricant in the formulation.

Because of the natural association of lubricant properties with lipophilic materials, formulations containing high levels of lubricant can show retarded dissolution of the active ingredient and the slow dissolution rate could adversely affect the in vivo bioavailability of the drug.

Lubricant study

Another important use of ejection force transducer is the evaluation of lubricants (either different chemically, or similar lubricants coming from different vendors).

As shown in Fig. 10, the preferred lubricant is No. 1 as it results in a smaller ejection force. Early lubricant studies are a must. When lubricant problems occur later on in the scale-up process, corrective measures not only require additional materials and development time, but may also require a supplement of an approved new drug application (NDA).

Response surface plot

Formulation and process optimization can be done statistically with the use of experimental design for estimates of the best processing parameters and excipient
and lubricant levels. Controllable variables in tableting are mainly the precompression and compression forces and tablet press speed, as well as the formulation component levels. Response variables include the ejection force, tablet hardness and friability, dissolution rate, and drug stability. The purpose of an experimental design is to perform a series of experiments in order to determine some levels of factors that will allow us to achieve an optimal level of dependent variables. The experiments should be designed so as to minimize effort and maximize statistical reliability of the results. Published work in this area deals mostly with response surface designs that produce a predictor polynomial equation for each response variable under consideration. A multidimensional surface is then searched for the best ranges of factor variables that, when plugged in the equations, result in the optimal value of the

![Fig. 8 Compactibility profile.](image1)

![Fig. 9 Lubricant profile.](image2)
responses. In this plot (Fig. 11), the optimal (highest) hardness is obtained when the compression force is in the range 3000–4000 lb with as much MCC in the formulation as possible.\textsuperscript{[67]}

Compactibility study—elastic recovery

Many powders, especially with viscoelastic compaction mechanism, such as starch or avicel, exhibit large degree of stress relaxation (with time-dependent deformation).

If you monitor punch displacement and compression force, you can make pretty accurate assessment of the compactibility of your material. If LVDTs are attached to both upper and lower punches, it is possible to actually measure in-die thickness of the tablet at various compression levels. In Fig. 12, one can see how the tablet thickness rapidly decreases in the compression stage and then gains some thickness during the decompression stage of the tableting cycle. The degree of this increase in
thickness is indicative of the elastic recovery as the pressure is removed from the tablet.

Elastic recovery and work of compaction were studied extensively using instrumented tablet presses.\textsuperscript{[68]}

Compactibility study—Heckel plot

In 1961 Heckel\textsuperscript{[69,70]} postulated a linear relationship between the relative porosity (inverse density) of a powder and the applied pressure. The slope of the linear regression is the Heckel constant, a material-dependent parameter inversely proportional to the mean yield pressure (the minimum pressure required to cause deformation of the material undergoing compression). Large values of the Heckel constant indicate susceptibility to plastic deformation at low pressures, when the tablet strength depends on the particle size of the original powder. The intercept of the line indicates the degree of densification by particle rearrangement (Fig. 13).

Typical problems in tableting include weight variation, capping, lamination, tooling irregularities, die binding, picking, and sticking. Most of such problems can be detected and/or resolved using proper instrumentation.

Upper and Lower Compression

Fig. 14 shows a typical set of upper and lower compression profiles. One can see that the lower trace is smaller than the upper. On a single station press, only the upper punch is usually moving, and the difference is caused, mainly, by the friction of the compressed powder inside the die.

On a rotary press, both punches are moving and therefore the friction of the punches inside the turret and the die causes the difference. The lower punch fits the turret with a larger standard clearance compared to the upper punch. In addition, the lower punch is never leaving the die, while the upper punch leaves and enters the die with each stroke. This results in a comparatively better alignment and lower friction. The close fit of the upper punch does not allow it to penetrate the die smoothly and this can cause the increase in friction. Thus, an excessive difference between the two peaks may indicate an underlubricated die or some punch misalignment problem.

Histogram of Punch Performance

Similar irregularities in punch tolerances become even more visible on a bar histogram where each bar corresponds to peak force produced by each punch (Fig. 15). As the new revolution arrives, the bar lengths...
are adjusted. If a particular bar persists in being taller or smaller than the rest, it means the presence of a long or short punch.

**Press Monitor—Real-Time Screen**

On this real-time screen (Fig. 16), one can clearly see that there is an abnormal ejection event in the first station after the proximity switch. This is a clear indication of a sticking punch or a similar problem. In addition, the first compression peak is somewhat taller than others. This may be caused by a long punch.

**Tablet Press Instrumentation for Process Scale-Up**

**Scale-Up Factors**

One of the main practical questions facing formulators during development and scale-up is: Will a particular formulation sustain the required high rate of compression force application in a production press without lamination or capping? Usually, such questions are never answered with sufficient credibility, especially when only a small amount of material is available and any trial and error approach may result in costly mistakes along the scale-up path.\[71\]
As formulations are moved from small-scale research presses to high-speed machines, potential scale-up problems can be eliminated by simulation of production conditions in the formulation development lab. One way to eliminate potential scale-up problems is to develop formulations that are very robust with respect to processing conditions. A comprehensive database of excipients detailing their material properties may be indispensable for this purpose. However, in practical terms, this cannot be achieved without some means of testing in production environment and, because the initial drug substance is usually available in small quantities, some form of simulation is required on a small scale. Studies of tableting process on a class of equipment, generally known as compaction simulators, are designed to facilitate the development of robust formulations. However, simulators are rarely used to simulate tablet presses for reasons that will be explained later.

In any process transfer from one tablet press to another, one may aim to preserve mechanical properties of a tablet (density, and, by extension, energy used to obtain it) as well as its bioavailability (e.g., dissolution that may be affected by porosity). However, a formulation that was successfully developed on a single station or small rotary press may not stand up to the challenges of scale-up because tablets that were meeting all specifications in the lab or clinical studies may exhibit capping or lamination at higher speeds.\[72,73\]

Compression force magnitude and the rate of force application are the most important variables in tableting scale-up.

**Force factor**

The compression force is the dominant factor of the tableting process. It is directly related to tablet hardness and friability, and is correlated with the phenomena of lamination and capping.

It was also shown to have effect on disintegration times and dissolution profile.

**Speed factor**

As the punch speed increases, so does the porosity of tablets and their propensity to capping and lamination. The tensile strength of compacts tends to decrease with faster speeds, especially for plastic and viscoelastic materials, such as starch, lactose, avicel, ibuprofen, or paracetamol. Such materials have the tendency to cap or laminate at higher speeds.\[74–88\]

The notions of dwell time and contact time, to be discussed in detail later, are the common indicators of press speed and the rate of force application.

**Force profile factor**

In addition to the level of force and the rate of force application, the shape of the compression force vs. time curve is of a paramount importance because it directly affects tablet properties such as hardness and friability. It is a known fact that the compression part of the compression cycle (during the “rise time” of the force–time profile) is 6–15 times more important than the decompression part as a factor contributing to capping and lamination. On the other hand, reducing the decompression part of the cycle results in the increase of tablet hardness by reducing the extent of elastic recovery.\[89\]

Alternatively, reducing the compression part of the cycle results in no change of tablet strength for viscoelastic materials and increased hardness for brittle materials.

**Other Considerations**

Numerous other factors may affect the scale-up process. The quality of the measurements, variation in tooling, powder properties, and tablet weight are some of those factors.

- Instrumentation grade.
- Measurement of speed.
- Measurements of mechanical strength.
- Tooling variation.
- Powder flow variation.
- Excipient/raw material variation.
- Tablet weight variation.

**Dwell Time and Contact Time**

Matching tablet press speed (rpm) of the research and production presses has, of course, no meaning, because of different number of stations and pitch circle diameter. It is vital, therefore, to translate the rpm into dwell time or contact time.

Many investigators have reported the effect of dwell times and strain rate sensitivity on the compaction of various excipients, especially viscoelastic materials.\[90–94\]

There are at least two definitions of dwell time in practice today.

**Functional definitions**

Functionally, the effective dwell time (EDT) at 90% level can be defined as the time it taken by the force–time curve
to traverse the 90% of the peak height. Likewise, the effective contact time (ECT) is the time between points at 10% of the peak height. The shape of the force curve depends, as we know, on the deformation mechanisms of the powder and therefore, all other variables being equal, EDT and ECT will be different for brittle and plastic materials. Although somewhat useful for material characterization, such variables should not be confused with the universally accepted definitions of contact time (time of contact) and dwell time (time of immobility).

**Mechanical definitions**

Mechanical Definitions of dwell and contact times disregard material properties and concentrate on press and punch geometry (Fig. 17). Contact time can be defined as the time the punch is in contact with the compression wheel. Dwell time is defined as the time the flat portion of punch head is in contact with the compression wheel (time at maximum punch displacement, or time when the punch does not move in vertical direction). In dwell time calculations, the length of the punch head flat and horizontal component of punch speed (as determined by RPM and pitch circle diameter) are used. In case of a round head tooling, the dwell time, as defined here, is zero. But it should be kept in mind that mechanical definition is given here as a convention, a yardstick, or a common measure, to compare press speeds for different presses, and its absolute value is meaningless. A proposed convention to quantify linear speed of a press is to use an Industrial Pharmaceutical Technology (IPT) Type B tooling with a known punch head flat as a standard for press speed comparisons.

In what follows, we will use the mechanical, rather than functional, definitions because they serve as an objective material-independent measure of compaction speed.

**Dwell time comparison for different presses**

Comparing the dwell time ranges for a number of presses can be a gratifying experience. Here one can see that even for the same brand name, there is a wide distribution of ranges. It has to be noted that proper scale-up will be possible only when the ranges overlap. Dwell time range may also be used to classify or identify tableting equipment. The dwell time ranges vary considerably in various tablet presses. As shown in Fig. 18, Manesty Betapress is positioned well within the range of production speeds of the high-speed presses. That is, probably, why this press is often used for R&D work. On the other hand, small presses such as Korsch PH106 or Piccola do not even come close to benchmark production speeds of 6 msec–15 msec in terms of dwell time. The MCC Presster™ can reach the production dwell times while making one tablet at a time.

**Dwell time vs. production rate**

For a benchmark production speed of 100,000 tablets per hour (Fig. 19), dwell time distribution follows an inverse power relationship, which is expected because dwell time is a reciprocal function of the press speed. In general, all production presses should be qualified with respect to dwell and contact times per benchmark output. Ideally, product development must be done on a laboratory press that can match (in terms of the dwell time) the target production output.

**Dimensional Analysis of Tableting Process**

Dimensional analysis is a method for producing dimensionless numbers that completely characterize the process. It is widely used in many areas, including chemical engineering and pharmaceutical industry. Because all
the dimensionless numbers necessary to describe the process in similar systems must have the same numerical value.\textsuperscript{[95]} matching such values on different scales is a sure way to success in any scale-up operation. This dimensionless space in which the measurements are presented or measured will make the process scale invariant.

In tableting applications, the process scale-up involves different speeds of production in what is essentially the same unit volume (die cavity in which the compaction takes place). Thus, one of the conditions of the theory of models (similar geometric space) is met. However, there are still kinematic and dynamic parameters that need to be investigated and matched for any process transfer.

Scientifically sound approach would be to use the results of the dimensional analysis to model a particular production environment to facilitate the scale-up of tableting process, by matching several major factors, such as compression force and rate of its application (punch velocity and displacement) in their dimensionless equivalent form.\textsuperscript{[96]}

**TABLET PRESS AND COMPACTION SIMULATORS**

It can be seen that, as a rule, tablets are formulated at speeds that are very slow compared to production. If
simulation of a production press is required to minimize the scale-up effort, some way of speeding up the tableting process in development is required. Once the linear speed of the punch is attained, the rate of force application (i.e., the instantaneous change in compression) should also be matched. This is, of course, an infinitely more difficult task.

Hydraulic Compaction Simulator

A small number of devices known as compaction simulators exist in the world. Invented more than 20 years ago, they become popular in basic compaction research. A wealth of studies have been generated in the last 20 years.[97–117]

Compaction simulators (Fig. 20) were designed to mimic the compression cycle of any prescribed shape by using hydraulic control mechanisms that are driving a set of two punches (upper and lower) in and out of the die. All hydraulic compaction simulators are similar in design and construction. A compaction simulator consists of several main units: the load frame (column supports and crossheads with punches), the hydraulic unit (pumps and actuators that move the crossheads), and the control unit (electronic console and computer). Usually, a simulator accepts F tooling only, but can be retrofitted to use standard IPT B tooling. Under computer control, the hydraulic actuators maintain load, position, and strain associated with each punch.

The simulation can be achieved by one of the two procedures: matching either the force (load control) or the movement of punches (position control) at any given moment of time. Thus, when running a simulator, one has a choice: to mimic the force/time path (compression profile) or the motion of the punches (punch displacement curves). It is impossible to mimic both at the same time on any hydraulic compaction simulator.

Load control profile

Matching the force–time profile of a production tablet press is the primary goal of any tablet press simulation. However, the rate of force application and the shape of the resulting signal are not usually known in advance. The compression profile (force vs. time) is impossible to calculate theoretically because it has a different shape for different materials and tooling.

Using an instrumented punch to collect force data is cumbersome because it is limited to a particular punch size and shape. Recalculation to pressure values is not always adequate. One can, however, monitor and record force waveform from a properly calibrated R&D grade compression transducer. Once the production press brand, model, speed, and tooling are specified, a waveform can be recorded and then fed into hydraulic simulator.

This approach is impractical for formulation development work because one would need to record force waveform on a rotary press using formulation similar to the one being developed. Usually, there is no such powder available and the actual formulation being developed is available in limited quantities.

Position control profile

Because load control profiles are not practical, users of hydraulic compaction simulators overwhelmingly prefer to utilize punch displacement profiles in hope that, once the punches are forced to move in the same pattern as in the production press, the force–time curve will follow. For example, a recently built laboratory compaction simulator does not have a force control functionality at all.[118]

There are three possible sources of the punch position trace:

- Prerecorded data.
- Artificial profiles.
- Theoretical profiles.
To obtain a position control profile from any tablet press, one has to record the movement of the punches using LVDT. Besides the technological challenge that this objective may present, the punch movements on a press depend on many factors, including brand name and model of the press, speed of the turret, shape of punches and die, size and shape of the tablet, and most importantly, compaction properties of the powder. The problem with this is that data from production presses are inevitably obtained using material other than the one being developed. It is a vicious circle: the profiles before developing a formulation and the formulation before obtaining punch displacement profiles are needed.

Many compaction studies were done on compaction simulators using artificial punch displacement profiles, for example, the so-called “single-ended” profile, i.e., when the lower punch is stationary (like in a single station press). Other studies were using a “saw tooth” profile, i.e., a constant speed profile where punch displacement speed is constant at any given time interval under load. It is obvious that such profiles have nothing to do with simulation, although they provide a degree of uniformity for basic compaction studies. The very name “compaction simulator” is a misnomer as is acknowledged by a number of researchers in the field. The machine is best described as a compaction research system because it is well suited for the basic compaction studies (densification and bonding properties of materials).

To simulate tablet presses, compaction simulator users most frequently employ the theoretical position control profiles. Theoretical path is calculated from the geometry of the press and punches, using the radius of the compression roll, the radius of the curvature of the punch head rim, the radius of the “pitch circle” (distance between turret and punch axes), and the turret angular velocity. 

The resulting sinusoidal equation is used in order to “simulate” punch movement in a tablet press.

In practice, theoretical and actual punch displacement profiles on a rotary press have very little in common because the theoretical profile does not account for several mechanical factors, such as punch head flat. Moreover, the punch movement equation was derived for a punch moving in and out of an empty die. The effect of material resistance to pressure and elastic recovery is not accounted for in the equation. The discrepancies between the calculated and real punch movements are rather striking. 

In addition, it was shown that the lower and upper punches may not move synchronously. Moreover, maximum force does not coincide in time with the minimum punch gap. These and other considerations (press deformation, contact time, etc.) make the effort of simulating a production press on a hydraulic compaction simulator rather impractical. That is why, to quote from a paper by Muller and Augsburger, “Although compaction simulator have been designed to mimic the displacement time behavior of any tablet press, they rarely have been used in that fashion.”

Literature sources reporting the use of compaction simulators in simulating actual tablet presses are rather scarce. Some studies suggest that, for whatever reason, tablets made on a Manesty Betapress were significantly softer than those made on a compaction simulator using the theoretical Betapress punch displacement profiles.

To summarize, one can say that hydraulic compaction simulators are ideally suited for basic compaction research but are not very practical for simulation of production presses.

Tablet Press Replicator: The Presster

Recently, a new type of machine was introduced to mimic production presses on a small scale. Known under a brand name of “Presster”—kind of an agglomeration of the words “press,” “presto,” and “tester”—this machine can be classified as a mechanical compaction simulator.

The Presster is a high-speed single station press that is also a tablet press simulator (Fig. 21). It was designed to simulate production presses without any use of hydraulic controls, and, consequently, there is no need to feed in any artificial, theoretical, or prerecorded punch displacement profiles. Built around a linear carriage that moves a set of punches and a die between two compression rolls, it can mimic press geometry by matching the compression wheels match press speed using a variable speed motor drive match tablet weight and thickness by adjusting depth of fill and the distance between the rolls match tooling by installing standard IPT or any special tooling.

Thus, using mechanical similarity, all of the scale-up fact are matched, namely, the compression force, the speed, and the shape of the force profile. To use Presster, first a production press to be simulate should be selected, and the compression wheels with a matching diameter should be installed. Then, production speed should be selected in terms of tablets per hour, RPM, or dwell time. The Presster will mimic the selected production press speed and compression force profile and will allow us to make one tablet at a time.

As a high-speed single station press, mechanical compaction simulator will be able to plot compressibility profiles, Heckel graphs, calculate work of compaction, and virtually any other imaginable variable that is of interest to formulators. Tensile strength of tablets made on a Betapress and The Presster was similar.
Precompression and ejection steps of the tableting cycle can be included in simulation. Some current limitations of Presster should be pointed out: It will neither follow any artificial punch movement profile, nor will it address, at least in its present implementation, the issues of feeding and die fill at high speeds, or speed-related temperature fluctuations.

PRESS INSTRUMENTATION AND CONTROL ON THE PRODUCTION FLOOR

Tablet Weight Control and Tablet Force Control

To keep tablet weight within the prescribed tolerance limits, the required instrumentation includes compression transducer and several proximity switches for station identification and pinpointing the compression event. Tablet weight controller can be just one, albeit a major, unit of a larger press automation system. Press automation system may include:

- Tablet weight control.
- Material handling interface.
- Feeding system.
- Collection system.
- Packaging system.
- Supervisory control (SCADA) station.

The latter can be a computer positioned on the supervisor’s desk that monitors the performance of each press on the production floor, with timely status report for each batch.

There are many reasons why it is imperative to control tablet weight variation:

- Production costs are lowered because there is less waste.
- Productivity is increased because there is a better equipment utilization.
- Batch-to-batch variability is minimized for obvious reasons.

When the cost of each out-of-spec wasted tablet is significant, the savings produced by weight control quickly add up. Product quality is improved when there is less of a chance to get an out-of-spec tablet into the acceptable batch. Last, but not least, is the improved safety because the automated process requires less human intervention.
Control mechanisms

For constant tablet thickness, in a small target area of tablet weight, compression force is directly proportional to tablet weight. Force control systems maintain compression force within prescribed limits by adjusting the depth of fill cam. The limits are established empirically for each formulation recipe.

Alternatively, a weight control system would require an expressed correlation between force and tablet weight. A few tablets at different force levels can be made to correlate the resulting tablet weights with the force values. Next, one can express tablet weight tolerance limits in terms of the compression force. The weight control system can adjust the dosing to keep the tablet weight within the desired limits. For this control theory to work consistently, one needs to recalibrate force–weight relationship periodically, as the powder properties and tablet mechanical condition can vary in time.

Control functions include alarm and shutdown (when any individual force peak or revolution average exceeds preset limits), force or weight control (usually done on revolution average only), and rejection of out-of-spec tablets. With a mechanical gate, usually several tablets are rejected at a time, with the bad tablet being rejected along with the adjacent good tablets. With a fast pneumatic–air stream rejection mechanism, the control system can pinpoint and reject one bad tablet only.

Control criteria

Control decisions are usually done as follows:

1. Adjust depth of fill cam if revolution average is outside some redefined acceptable limits.
2. Reject each tablet that exceeds individual limits or if the press speed slows down beyond some level.
3. Sound an alarm if the same station repeatedly produces bad tablets or if revolution average exceeds alarm limits.
4. Shut down the press if any tablet is made with a force exceeding the shutdown limits, or if revolution average is outside the shutdown limits.

Control algorithms

One-point control is a description of a control when any deviation of the compression force from a preset target level results in a corrective action of the dosing cam. This action can be proportional (P) to the deviation from the target, or it could be correlated with the integral (I) of the deviation over some time, or it could be tied in with the rate of change (D, for derivative) of the compression force. This would correspond to proportional, integral, or derivative control types, respectively. There also can be a combination of the control types. Thus, one can have P, I, P + I, P + D, and P + I + D control algorithms.

Alternatively, a two-point control is enacted when the compression force is outside an acceptable band outlined by the upper and lower tolerance limits. Thus, there are separate control limits, rejection limits, alarm limits, and shutdown limits, and no respective action is taken when the signal is inside these limits.

Strictly speaking, one-point control can be viewed as a special case of the two-point control when the bandwidth of the control limits is tightened to approach zero.

Control Systems

Original equipment manufacturer (OEM) control systems

Almost each tablet press manufacturer offers a system that is designed to control the press. Some of these systems are very sophisticated devices that monitor and control a vast array of tableting functions. If, however, there are several brand names on the production floor, any standards in the control system implementation for different manufacturers should not be expected. Likewise, software interfaces exhibit quite a range of user-friendliness.

In one brand name press, tablet weight control is achieved by regulating the dosing cam based on powder bed thickness in the precompression cycle. This clever approach is possible because precompression force is kept relatively constant by means of pneumatic compensating mechanism. Under these conditions, tablet weight is directly proportional to thickness. The subsequent compression cycle can be done to constant thickness, like on any other press.

Generic control systems

An alternative to OEM control systems is generic controllers that may offer plug-in compatibility with the brand name controllers and may provide a degree of standardization.

However, such generic controllers may lack the degree of sophistication and versatility of the controllers that are made by the press manufacturers. One thing to keep in mind is that not all control systems are created equal, but all control systems use the same principles.

A decent tablet weight control system should be based on product recipes, provide instant display of compression force distribution, control charts and batch reports on
-demand, archiving data for subsequent analysis or documentation, give some measure of standardization, be fully compliant with current validation requirements, and provide a multilevel security, e.g., password protection for operator and supervisor when they need to change recipes, etc. Some examples of displays, available to operators of instrumented production presses equipped with controllers, follow.

Recipe example

In Fig. 22, an example of a typical control recipe with dosing cam adjustment, rejection, alarm, and shutdown limits expressed as a percent deviation from the target tablet weight is shown. The software then converts all values into the corresponding compression force levels for control purposes.

Bar histogram

This chart is similar to one used in tablet press monitoring for press troubleshooting (Fig. 15). It is vital for any production press operator.

Control chart

Control chart is a simple graph of peak compression force vs. time. Each point on the chart corresponds to the
average of \( N \) tablets made, with \( N \) ranging from 1 to several revolutions. The horizontal lines would indicate the control limits.

Statistical process control chart

Statistical process control (SPC) chart (Fig. 23) of the averages is another “must have” real-time display. Each point on the chart represents a revolution average of the compression forces or corresponding tablet weights. The limit lines are calculated at one standard deviation of the mean, and there are certain rules that are used to determine when and if the process gets out of control. These rules are available in any textbook on the SPC.

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