

The role of compaction simulator equipment in formulation design

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ABSTRACT

The assessment of the compaction performances of pharmaceutical powders is an important aspect of tablet product design, development and manufacturing. Compaction simulators have potential applications in pharmaceutical research and development in terms of studying basic compaction mechanisms, troubleshooting, various process variables, compaction data library creation, scale-up parameters, and fingerprinting of new active pharmaceutical ingredients (APIs) or excipients. The upscaling of the compaction process between early R&D and production can be time-consuming and costly, resulting in a long time-to-market and shorter commercial lifecycles. Due to the limited availability and high price of a new APIs during early drug development phases, compaction simulators have proven highly valuable as the dwell time and punch speed can be set accurately to mimic bottom and upper punch movement on a rotary tablet press.

Many issues inherent in the formula ingredients or acquired from previous processes can be avoided or reduced if applied correctly. However, if adequate attention is not paid to understanding the compaction behaviour of what is being pressed, this process may also be the source of several other problems. Pharmaceutical scientists now use a variety of instrumented presses to produce robust tablet formulations. They allow scientists to conduct experiments for in-depth analysis of compaction characteristics of pharmaceutical materials with great efficiency in terms of time, expense, and knowledge gained. The ability to use simulators for anything from early formulation studies to manufacturing troubleshooting makes them invaluable, particularly in light of the recent Process Analytical Technology (PAT)/Quality by design (QbD) phenomenon.

Keywords: Compaction, compaction simulator, tablet press simulator

INTRODUCTION

Compaction is one of the most crucial unit operations in the pharmaceutical industry because it determines physical and mechanical properties of tablets such as strength and density (friability/hardness). The tablet compression process has an effect on dosage form integrity and bioavailability. Tablet compact production is a complicated process involving several variables and a variety of engineering principles, and a thorough understanding of compression physics is still a work in progress (Mohan, 2012).

There are several types of equipments that carry out powder compaction in the pharmaceutical area, in particular, these include the single-press, the rotary-press and the compaction simulator (Çelik & Marshall, 1989). Instrumented tablet punching devices, instrumented punches/dies, and compaction simulators can all be used to investigate mechanical aspects of tablet formation.

Compaction simulators have potential applications in pharmaceutical research and development in the study of basic compaction mechanisms, troubleshooting, various process variables, compaction data library creation, scale-up parameters, and fingerprinting of new APIs or excipients.

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Description and types of compaction simulator

Compaction simulation is an integrated compaction research system, which has been of scientific interest since the 1970s, with the first compression simulator described in 1976. The aim of compaction simulation is to be able to simulate industrial compression – that is, to be able to predict which parameters to apply to industrial equipment to obtain the desired properties in a tablet (Moulin & Kowalski, 2019).

Compaction simulators are defined as devices capable of mimicking in real-time, the exact cycle of any tablet press and recording the parameters. It enables a new approach in tableting research and is used to study powder compaction behaviour and fundamental material characterization using different compression parameters such as compression force and punch displacement (Reugger & Celik, 2016).

They are multifunctional equipments that can assist in all phases of the pharmaceutical industry's drug development and production (Celik, 2016; Celik and Marshall, 2010; Michaut et al., 2010).

Advantages and disadvantages of compaction simulators

Compaction simulators (Figure 1) have many benefits, including the ability to evaluate the following: tablet properties (strength, disintegration, and dissolution) under identical manufacturing conditions (since each individual tablet's compaction history is known); the ability to evaluate small amounts of material; basic compaction mechanisms; scale-up parameters; fingerprinting of actives, excipients, and formulations; build-up effects such as adhesion problems (much easier with mechanical rotary machine due to number of tablets produced per hour); the effect of process variables (speed, etc.); the effect of tooling variation.

The following are some of the most well-known drawbacks of all compaction simulators: While the available systems have paddle feeding systems, they cannot directly replicate the effect of the force feeder on a rotary tablet press; while basic machine operation is simple to learn, full machine use necessitates expertise in data manipulation and analysis; the effect of bulk flow on the rotary tablet press cannot be simulated; the centrifugal force caused by the turret rotation cannot be simulated (Celik 2016).

Types of compaction simulators

Compaction simulators are mainly divided into two categories:

1. Hydraulic compaction simulators
2. Mechanical compaction simulators
 - a. Mechanical linear compaction simulators
 - b. Mechanical rotary cam compaction simulators (Medelpharm, 2021)

Mechanical rotary cam compaction simulators (Stylcam)

The mechanical rotary cam compaction simulator (Stylcam, Medelpharm) is set up as a single station eccentric tablet press with two punch holders, with both punches following a programmable electronic cam that simulates a rotary tablet press.

A revolving cam guides the movement of each punch holder. During the pre-compression and compression stages, the upper and lower punches are designed to travel in a symmetrical manner. Strain gauges in the upper and lower punch holders track the pressure on the upper and lower punches. The measurement of punch movement is made simpler by two displacement captors positioned on both the upper and lower punch holders (Medelpharm, 2021).

The two cams are mechanically synchronized and powered by a programmable motor that accelerates or stops to adapt the punches' movement. The Compaction Simulator can simulate the compression timings of any rotary press (including relaxation and, for most presses, ejection timing) and record all important parameters throughout the cycle (Celik & Marshall, 1989). Moving the upper and lower cams together or farther apart, similar to the rolls on a rotary press, adjusts the main compression force or tablet thickness (Celik, 2016).



Figure 1. Image of Stylcam 200R; mechanical rotary cam compaction simulator (Jiwa, 2020).

The device can run at a constant speed or the cycle's speed can be modulated during operation. This adaptability enables the simulation of various rotary tablet presses. No parts are needed to be changed to simulate various presses because the tablet press profiles are built into the device. Filling height, ejection height, pre-compression force, main compression force, and speed can all be adjusted. A transducer mounted on the feeding shoe senses the force needed to separate the tablet from the punch surface and can be used to measure tablet take-off force. Its ability to produce small batches of tablets in an automated mode adds to its versatility (Celik, 2016).

Using a compaction simulator, tablets are prepared under restricted conditions, for instance, the punches can be controlled and varied considerably. There are various applications that can be served through such machine. For example, the sensitivity of the drug to such variations (such as force) can be investigated. In addition to, the loading pattern of production presses can be mimicked in order to predict any future scale-up obstacles that may be present by using only small quantities of the materials needed (Jain, 1999).

Benefit of compaction simulator in the pharmaceutical area

Some benefits of the use of compaction simulator in the pharmaceutical area are as follows (Celik & Marshall, 1989):

- The effect of process variables (speed, etc.) can be determined.
- The effects of tooling variations, such as tooling type and punch shape can be studied.
- Scale-up parameters, such as type of press can be investigated.
- Build up effects such as adhesion problems.
- Basic compaction mechanisms can be determined, and the robustness of the formulation can be tested at high speeds (for different tablet presses).
- Tablet properties (strength, disintegration, dissolution) under identical manufacturing conditions can be tested (since the compaction history of each individual tablet is known).
- Fingerprinting of actives, excipients and formulations if possible.
- The effects of drug substance, excipient, or process change can be predicted.

Practical applications of compaction simulators

Compaction simulators can be used in practical applications in different phases of product development and manufacturing in the pharmaceutical area as seen in Figure 2 (Celik & Marshall, 1989):

Evaluation of compaction simulator data in the pharmaceutical area

Simulators have the ability to reproduce upper and lower punches displacement profiles in order to get information about powder compressibility (Celik, 2016). Compressibility profiles, which are functions of solid fraction *versus* applied pressure, are used to explain the fundamental mechanical behaviour of powders during compaction. These functions, which are collected during compression (in-die) or post ejection (out-of-die), show how much pressure is required to compress a given powder formulation to a given density or thickness. Several studies have been completed using a compaction simulator to evaluate powder compressibility by evaluating tensile strength values at different compaction forces (Al-Karawi et al., 2002; Arida and Al-Tabakha, 2008; Dudhat, Kettler & Dave, 2017; Muzíková & Zvolánková, 2007; Ruegger and Celik 2000; Wang, Wen, & Desai, 2010; York & Pilpel, 1973).

Data acquisition software (ANALIS, Medelpharm) allows you to construct comprehensive individual analyses, operating with single data points during a compression period or exploiting average values during batch processing, using standard reporting parameters like Heckel, force hardness ejection force, and, others. Studies on ejection force values produced by compaction simulator give insight into lubricant efficiency and optimization of lubricant concentration which is beneficial for formulators (Khan & Rhodes, 1976; Paul & Sun, 2018; Salpekar & Augsburger, 1974; Sun, 2015). A compaction simulator has the ability to perform Heckel Analysis which assists in characterizing the deformation behavior of materials using a simulator which gives better understanding of pharmaceutical excipients (Ozalp, Onayo, & Jiwa, 2020; Sun & Grant, 2001). Elasticity/plasticity, work of compaction, and time-dependent deformation behaviour of pharmaceutical powders are described using mathematical models, force-distance (De Blaey & Polderman, 1971; Moulin & Kowalski, 2019; Ragnarsson & Sjögren, 1985; Tay, Sun, & Amidon, 2019) force-time, (Leitritz, Krumme, & Schmidt, 1996; Yliruusi, 1997) and die-wall force parameters of tablet manufacturing produced by compaction simulator data (Hoblitzell, & Rhodes, 1990).

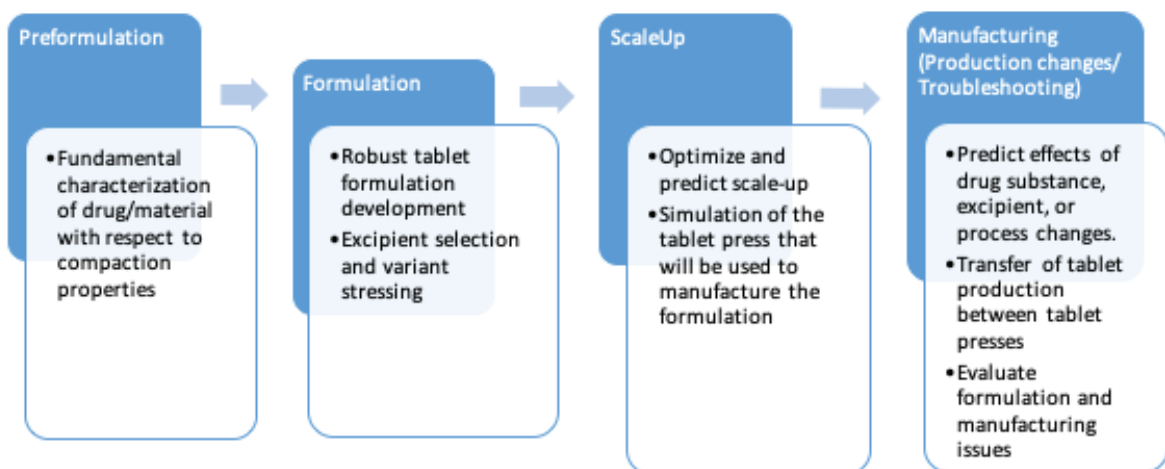


Figure 2. Illustration of practical applications of compaction simulators in the pharmaceutical area.

A compaction simulator produces force-displacement (F-D) curve data in order to evaluate the amount of energy used during the tableting process, as seen in Figure 3 below. Due to variations in packing characteristics of individual formulation powders, the work of compaction provides a thorough assessment of the characteristics of tableting parameters, as shown by the F-D curve. Different plastic and elastic deformational properties, as well as different packing characteristics, absorb different quantities of energy, as shown by variations in compaction energy (Ozalp, Chunu, & Jiwa, 2020).

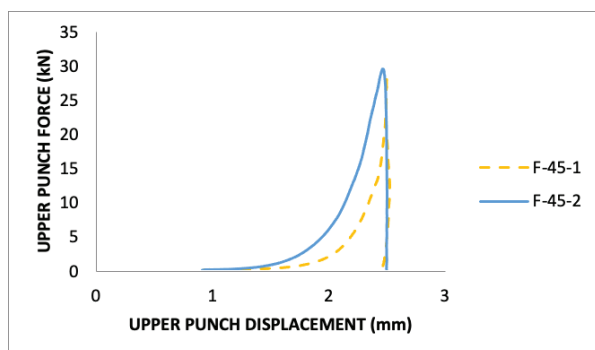


Figure 3. F-D curve for two different formulations, produced by compaction simulator (Ozalp et al., 2020).

The porosity and pressure are determined using an instrumented tableting presses or a compaction simulator, which allows the punch displacements to be measured simultaneously with the compressive forces (Celik & Marshall 1989; Cook & Summers, 1990; Duberg & Nyström, 1985; Jiwa, 2020; Newton & Grant, 1974; Nordström et al. 2013; Van der Voort Maarschalk & Bolhuls, 1999; Van Veen et al., 2000).

Figure 4 shows porosity plots of two pure fillers at varying compaction pressures produced by compaction simulator data. In-die porosity measurements give insight into powder compactability and volume reduction during the compaction process, which assist formulators in selecting suitable excipients (Jiwa, 2020).

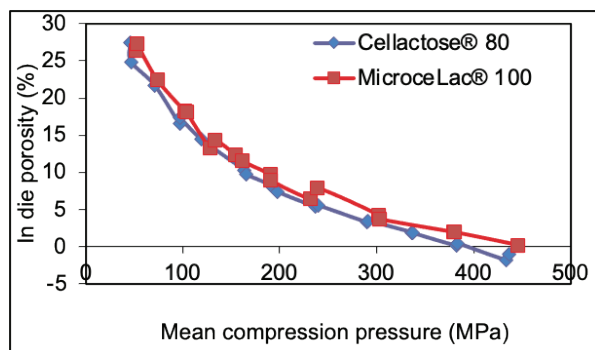


Figure 4. In die porosity (%) of pure Cellactose® 80 and MicroceLac® 100 at compression pressures between 5MPa and 450MPa (Jiwa, 2020).

Excipient research and fundamental material characterization with respect to compaction properties

The compaction simulator is a good tool to test the functionality and performance of excipients as well as characterise tableting properties of powders. Simulators can be used to compare the compaction behaviour of different materials (excipients, APIs, formulations) in addition to evaluation of compressibility, deformation mechanism of powders both as pure materials and in formulations to determine the characteristics of the material (Busignies et al., 2006; Busignies et al., 2012; Heinz et al., 2000; Muzíková, & Zvolánková, 2007).

A recent study was carried out to characterize the behaviour of two fillers by observing the ejection force data produced by compaction simulator at compaction pressures between 50-450MPa (Figure 5) (Jiwa, Aksu, & Ozalp, 2020).

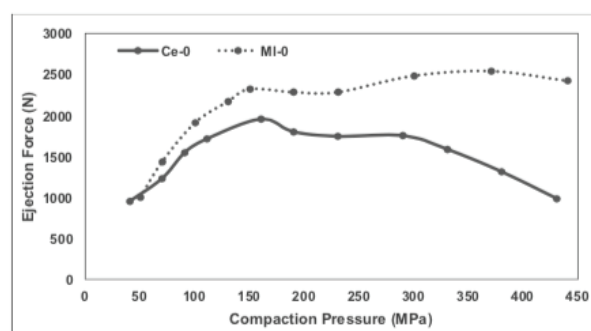


Figure 5. Comparison of ejection force data of pure Cellactose®80 (Meggle) and MicroceLac® 100 (Meggle) produced by a compaction simulator (Nailla, 2020).

Some models are used for compact production to classify tablet excipients. The predominant behaviour of powder densification and deformation (plastic, brittle and elastic) can be determined using simulators (Picker, 2000). Data from the Heckel study can be obtained using two methods, the tablet-in-die method (at pressure) and the ejected tablet method (at zero pressure) (Fell and Newton 1971; Heckel 1961). As seen in Figure 6, the compaction simulator readily produces in-die Heckel plots in order to evaluate powder densification and deformation characteristics of excipient. This gives insight for formulators when selecting excipients (Ozalp et al., 2020).

Formulation research and robust tablet formulation development

Simulators are used to develop formulation rules for selection of excipients. They assist formulators in the assessment and study of the effects of different methods for massing, drying, and blending as well as adjusting process parameters to obtain a robust formulation. New and robust formulations for manufacturing can be developed using compaction simulator in order to optimize the excipients, as well as amounts used. A study was completed in order to improve the compressibility and tablet characteristics of Paracetamol using both filler and binder using a compaction simulator. Results of tensile strength for different formulations seen in Figure 7 give insight into compactability of excipients at different compaction pressures (Ozalp et al., 2020).

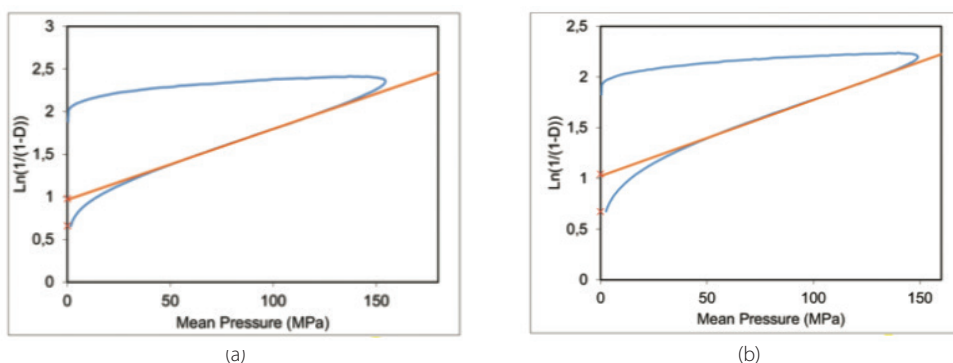


Figure 6. In-die Heckel plot for pure (a) StarLac® and (b) FlowLac®10 compressed at 150 MPa (Ozalp et al., 2020).

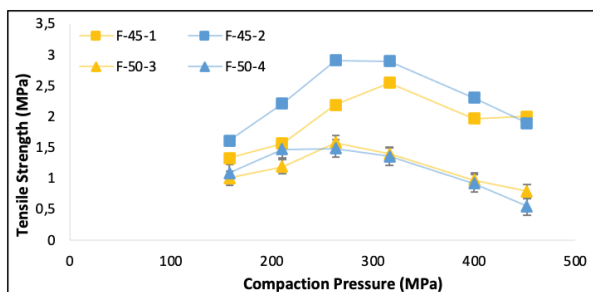


Figure 7. Tensile strength of formulations containing different concentrations of excipient combinations at different compaction pressures (Ozalp et al., 2020).

During formulation, a formulator should keep in mind that the speed and amount of pressure applied will almost certainly affect the formulation's compaction behaviour. As a result, for a given model of a given press, the formulation should ideally be run at a variety of speeds and pressure levels. Simulators are extremely useful for determining the impact of punch velocity on the compaction properties of powders in order to develop a robust formulation (Michaut et al., 2010; Tye & Sun, 2015). For problematic formulations in industrial production, compaction simulator is used as a troubleshooting tool in order to better understand and solve tableting problems (e.g., capping, lamination, lubrication etc.) (Sun, 2015).

Simulation of the tablet press that will be used to manufacture the formulation

The compaction simulator has the ability to establish whether a particular formulation has scale-up potential. It is used to evaluate the transferability of product properties (such as tensile strength and porosity) from a compaction simulator to various scales of rotary presses for common pharmaceutical ingredients. To smoothen the transfer process, crucial process and system parameters can be defined and clarified. (Heinz et al., 2000; Natoli et al., 2017; Wünsch et al., 2020).

Transfer of tablet production between tablet presses

Manufacturers occasionally require tablet production to be transferred between machines as they aim to increase production or replace older equipment with newer models. Due to the complicated powder mechanics involved in tableting, any changes in process that increase speed, duration, or compression force will cause a tablet formulation to fail to operate

successfully on new equipment. Even minor changes to tooling design may affect powder compaction properties, leading to tablet failure due to capping or lamination (Dudhat et al., 2017). Simulators have the ability to evaluate changes in compatibility that can occur when transferring a substance from one machine to another, as well as decide alternate ingredients that may be used in a formulation (Celik, 2016).

CONCLUSION

Continuous manufacturing technologies deliver major advantages in terms of time and cost savings, flexibility, efficiency, and environmental impact during the manufacture of oral solid dosage forms. As a result, these technologies have piqued the attention of the pharmaceutical industry. Compaction simulators are one of the most integrated and versatile tableting research tools available; they allow scientists to conduct experiments for in-depth analysis of compaction characteristics of pharmaceutical materials with minimal time, expense, and knowledge gained. The ability to use simulators for anything from early formulation studies to manufacturing troubleshooting makes them invaluable, particularly in light of the recent PAT/QbD phenomena.

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