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Toward predicting tensile strength of pharmaceutical tablets by ultrasound measurement in continuous manufacturing

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ABSTRACT

An ultrasound measurement system was employed as a non-destructive method to evaluate its reliability in predicting the tensile strength of tablets and investigate the benefits of incorporating it in a continuous line, manufacturing solid dosage forms. Tablets containing lactose, acetaminophen, and magnesium stearate were manufactured continuously and in batches. The effect of two processing parameters, compaction force and level of shear strain were examined. Young's modulus and tensile strength of tablets were obtained by ultrasound and diametrical mechanical testing, respectively. It was found that as the blend was exposed to increasing levels of shear strain, the speed of sound in the tablets decreased and the tablets became both softer and mechanically weaker. Moreover, the results indicate that two separate tablet material properties (e.g., relative density and Young's modulus) are necessary in order to predict tensile strength. A strategy for hardness prediction is proposed that uses the existing models for Young's modulus and tensile strength of porous materials. Ultrasound testing was found to be very sensitive in differentiating tablets with similar formulation but produced under different processing conditions (e.g., different level of shear strain), thus, providing a fast, and non-destructive method for hardness prediction that could be incorporated to a continuous manufacturing process.

1. Introduction

There are many advantages to Continuous Manufacturing (CM), including: (i) integrated processing with fewer steps, which results in minimal manual handling and increased safety; (ii) smaller facilities (i.e., reduced cost); and (iii) on-line monitoring and control for enhanced product quality assurance in real-time (Chatterjee, 2012). Many industries, such as petrochemical and food technologies, have shifted to CM. However, in the pharmaceutical industry, products are still manufactured mainly in batches. The major barriers to CM are traceability and the lack of rapid techniques for quality assurance and control. In an attempt to explore and address the manufacturing issues in the pharmaceutical industry, the U.S. Food and Drug Administration (FDA) has released the Process Analytical Technology (PAT) initiative. Designing and developing rapid techniques and ultimately improving the quality of pharmaceutical products are the goals of the PAT initiative (FDA, 2004).

Among pharmaceutical products, tablets are the most common dosage form due to their high production rates, acceptable shelf life, dosage accuracy, and controlled drug release. The mechanical strength of tablets is an important quality attribute that is consistently tested to ensure that tablets can withstand post-compaction operations, such as coating, handling, and storage. The dissolution profile of a drug tablet is also influenced by its mechanical properties (Saravanan et al., 2002). Lubrication, among other factors, may significantly affect the mechanical properties of tablets (Johansson, 1984). Lubricants are an essential ingredient in tablet formulations to prevent powders from sticking to the tooling and improve powder flow properties during the compaction process (Moody et al., 1981). Concentration of lubricant and exposure to shear are two important variables in the lubrication process. A significant reduction in tablet hardness due to overlubrication with magnesium stearate (MgSt), for example, has been previously shown (Bolhuis et al., 1975; De Boer et al., 1978; Bossert and Stains, 1980; Kikuta and Kitamori, 1994), and is caused by the formation of an MgSt film on powder particles, which weakens the interparticle bonding (Bolhuis et al., 1975; De Boer et al., 1978).

The mechanical strength of tablets is typically measured by traditional destructive tests, such as three-point bending, four-point bending, diametrical compression, and axial tensile strength tests (Stanley, 2001; Podczeck, 2012). These destructive tests not only damage the tablet structure and cause loss of product, they also provide limited information about the mechanical state of a tablet.

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Moreover, the time spent to test the tablets destructively is in the order of minutes, which is not suitable for an on-line monitoring process. Ultrasound (US) testing has been recently introduced as a fast, non-invasive technique to measure tablet strength. This requires measuring the time of flight (TOF) of a low intensity mechanical wave propagating in the tablet. The Young's modulus (E) can then be calculated by determining the longitudinal speed of sound (SOS) of this transmitted US signal from the TOF measured in a tablet of known thickness (Akseli et al., 2009). Hakulinen et al. (2008) have observed that SOS decreases as the porosity of the tablet increases. In addition, the SOS in a tablet was found to increase with its tensile strength (Akseli et al., 2011; Simonaho et al., 2011). The ease of implementation, fast computing time, and low cost of this method make it possible to be placed on-line for real-time mechanical characterization of tablets. Leskinen et al. (2010) have introduced an in-die US measurement system by incorporating US transducers inside the upper and lower punches. US attenuation was found to be a good approach to detect defective tablets. In a later study, they measured the SOS in binary mixtures (i.e., mixtures of an active ingredient with an excipient) during tableting using the same system. They found that SOS is sensitive to the mixing time of magnesium stearate and the dwell time of the compaction cycle (Leskinen et al., 2013). The in-die real-time tablet monitoring system has also been used by Stephens et al. (2013) to evaluate the tablet mechanical integrity and the presence of defects, and its applicability as a control system was validated. Although the in-die measurement provides valuable information, the mechanical strength of a tablet is different if measured out-of-die. After compaction and in-die unloading the tablet experiences ejection forces, as well as radial and axial elastic relaxation, which might significantly affect the mechanical integrity of the tablet (Train, 1956; Long, 1960; Maarschalk et al., 1998).

In this study, we focused on evaluating the mechanical integrity of tablets after compaction via US testing. Cylindrical tablets were prepared either continuously or in batch. The formulation was kept constant (90% lactose monohydrate, 9% acetaminophen (APAP), and 1% MgSt), while the compaction force and level of shear strain varied. US testing was used to evaluate the strength of tablets by measuring the TOF. The tensile strength of the same tablets was then determined using a mechanical hardness tester. It was observed that, as the blend was exposed to an increasing level of shear strain, the speed of sound decreased and the tablets became both softer and mechanically weaker. It is also noticed that in order to predict the hardness of a tablet, two properties should be taken into account: Young's modulus and relative density. A strategy for hardness prediction is proposed that uses the existing theoretical/semi-empirical models for Young's modulus and tensile strength of porous materials. Overall, US testing is found to be a reliable technique to predict the variation of tablet strength with processing conditions.

2. Materials and methods

2.1. Materials

Lactose (monohydrate N.F., crystalline, 310, Regular, Foremost Farms USA, Rothschild, Wisconsin, USA), acetaminophen (semi-fine, USP/paracetamol PhEur, Mallinckrodt, Raleigh, North Carolina, USA), and magnesium stearate N.F. (non-Bovine, Tyco Healthcare/Mallinckrodt, St. Louis, Missouri, USA) were used as purchased. A formulation containing 90% lactose, 9% acetaminophen (APAP), and 1% magnesium stearate (MgSt) was prepared on a weight basis in both batch and continuous production. The true density was measured with five parallel measurements with a pycnometer (AccuPyc 1340, Micromeritics) using helium as the measuring gas. The nominal particle sizes and true densities of the materials used are listed in Table 1.

Table 1
Blend constituents, nominal mean particle size, and true density.

Material	Mean particle size (μm)	True density (g/cm^3)
Lactose	180	1.56
Acetaminophen (APAP)	45	1.30
Magnesium stearate	10	1.04

2.2. Continuous manufacturing

The pilot plant employed for continuous manufacturing is situated at the Engineering Research Center for Structured Organic Particulate Systems (ERC-SOPS), Rutgers University. A detailed description of this plant can be found in Singh et al. (2014). There are four main unit operations when tablets are produced by direct powder compression: feeding, delumping, blending, and compacting. We present here a brief overview of each of these operations:

Feeding and delumping: First, from gravimetric feeders (K-Tron KT20) APAP and lactose were separately fed into a mill (Quadro Comil 197-S). The MgSt was added after the mill to prevent over-lubrication of the formulation.

Blending: The blend was then sent to a continuous blender (Glatt GCG-70) with a speed set at 200 rpm. Chemical composition of the powder was monitored using a Bruker Matrix near-infrared (NIR) spectrometer.

Compaction: The desired formulation was sent through a hopper into a fill-o-matic system with a speed set at 25 rpm. Finally, the blend was compressed using a 36-station Kikusui Libra-2 double layer tablet press with a 10 mm tooling at a compaction speed of 20 rpm.

The overall flow rate and the tablet weight were set to 20 kg/h and 350 mg, respectively. The tablets made in the continuous line will be referred to as *continuous* tablets. The compaction force (F_c) was varied during the run by changing the distance between punches. Since the individual F_c values are not recorded for each tablet, we categorize the tablets based on their nominal compaction force values (F_n). Tablets were collected after all the processing parameters reached steady state. Six different nominal force (F_n) settings were selected ranging from 8 to 28 kN. Twelve tablets for each of 8, 20, and 28 kN and eighteen tablets for each of 12, 16, and 24 kN F_n conditions were analyzed.

2.3. Batch production

2.3.1. Blend preparation

Two different powder mixing equipments were used in the batch production of tablets: a V-blender (Patterson-Kelley Co., East Stroudsburg, PA) and a laboratory scale resonant acoustic mixer (labRAM) (Resodyn Acoustic Mixers, Butte, Montana, USA).

In the V-blender mixer, a 15-minute pre-blending step was applied at a rotation rate of 15 rpm to reduce the stickiness of APAP and improve its flowability. MgSt was added and mixed with the blend for 2 additional minutes. The blended powder was then unloaded from the V-blender and subjected to a controlled shear environment in a modified Couette cell at a shear rate of 80 rpm. For additional information about this instrument, the reader is referred to Mehrotra et al. (2007) and Pingali et al. (2011). Three different shear strain environments were selected in this study: 0, 160 and 640 revolutions, corresponding to 0, 2, and 8 min in the shear device. As we increase the number of revolutions in the shear cell, the degree of MgSt coverage on the particles increases. The tablets made using this mixing method will be named according to the