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Rapid method for measuring the mechanical properties of pharmaceutical compacts

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ABSTRACT

A rapid technique to measure the mechanical properties of pharmaceutical tablets is presented. The Young's modulus of elasticity and Poisson ratio are determined by fitting the measured transient force, generated by the impact of tablets with a dynamic load cell, by the theoretical force predicted from a Hertzian spring-dashpot model. Results of the method applied to a series of pharmaceutical compacts having different porosities and prepared from different excipient blends, demonstrate good agreement between the calculated force and the measured force. In particular, the Young's modulus and Poisson ratio calculated for a 22% porous microcrystalline cellulose compact are 3.5 GPa and 0.34, respectively. As the total measurement time is less than 100 μs, the technique can be used as an in-line process measurement for manufacturing process control.

1. Introduction

Appropriate mechanical properties of pharmaceutical tablets are essential to their process and product performance. Throughout manufacturing, tablets must be able to withstand the mechanical stresses imposed by handling, transport and packaging. Similarly, tablet efficacy, such as the active pharmaceutical ingredient release rate, can be affected by the tablet mechanical properties [1]. Formulators must balance the various mechanical property requirements to achieve suitable tablet performance. Due to process variability, it may be desirable to confirm that each tablet meets the target mechanical specifications. However, the instruments used for such measurements during development are often manually intensive and incapable of operating at the rates required for in-line process measurements. Thus, there is a need for an automated, rapid measurement technique that can be readily integrated into manufacturing for in-line process control of tablet mechanical properties.

Near infrared spectroscopy (NIR) [2–6], pulsed acoustics [7,8], and photoacoustics [9] are several nondestructive techniques that have been investigated for in-process tablet mechanical property measurements. NIR techniques are convenient, as NIR measurements are often performed to evaluate the content uniformity of tablets [7,8]. In NIR techniques, the tablet hardness is indirectly determined from empirical models applied to spectroscopic measurements, which often require relatively long acquisition times compared to tablet manufacturing rates [10]. In photoacoustic techniques the modulus is calculated from the velocity of pressure waves generated by a laser. However, the requirement of a mega-watt laser hinders the integration of a suitable instrument into a manufacturing process [9]. Pulsed acoustic measurements are both rapid and relatively simple. In pulsed acoustics, the tablet modulus is calculated from the velocity of pressure waves generated from piezoelectric transducers, which have been implemented in other pharmaceutical manufacturing processes [11].

An alternative, simple in-process method to acquire data on tablet properties is to quantitate the impact dynamics that tablets experience during manufacturing. The analysis of the transient forces that occur during impact phenomena are employed in a diversity of applications to provide product or process information [12–15]. Related techniques have been previously reported for examining pharmaceutical samples. For instance, Bharadwaj et al. [16] calculated the coefficient of restitution (COR) from the rebound height of pharmaceutical compacts impacting a horizontal planar surface. The COR was found to be related to the compact composition, and was postulated to be a material dependent parameter that could be used to predict processing characteristics. An extension of this idea is to measure the transient impact force from the collision of tablets against suitable substrates, from which it may be possible to quantitatively extract tablet mechanical properties.

Extracting mechanical properties from dynamic impact force measurements requires solving the equations of motion with appropriate rheological constitutive equations for the colliding bodies. The abundance of literature pertaining to the collisions of granular pharmaceutical materials [17,18] suggests that the Hertzian spring-dashpot (HSD) may be applicable to compacts of common pharmaceutical excipients. The goal of this work is to demonstrate that two key mechanical properties (Young's elastic modulus, and Poisson ratio) of

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model pharmaceutical compacts can be rapidly and accurately extracted from dynamic impact force measurements with sufficient speed that this approach can be used for in-line process control.

2. Theory

In these experiments, the mechanical properties of pharmaceutical compacts are determined by fitting the measured transient impact force to the theoretically predicted force for a compact striking a planar surface. For a one-dimensional collision, the dynamics of the compact are defined by the equation of motion [17,19–23]:

$$\frac{d^2}{dt^2}(mx) = \sum_i F_i \tag{1}$$

Here, x is the coordinate position of the compact center of mass with the origin set at the surface of the plane, m is the compact mass, and F_i is the ith force acting on the compact. The calculation is facilitated by relating the position coordinate to the compact deformation, δ, by:

$$\delta = (R - x)H(R - x) \tag{2}$$

Where R is the undeformed compact radius and H is the Heaviside step function.

The forces relevant for the experiments conducted in this work include a gravitational body force, an elastic surface force, a viscous force representing the dissipation of energy due to recoverable tablet deformation, and possibly a yield force that includes additional dissipative losses due to unrecoverable plastic deformations. The material forces, which are determined by the rheological constitutive equation relating the compact stress to the compact deformation, are key to accurately predicting the compact properties.

If the duration of the impact is long compared to the period of vibration of the acoustic pressure wave within the compact, then a quasi-static approximation can be used to relate the compact deformation to the instantaneous elastic stress distribution. Additionally, for a sufficiently low velocity impact, the maximum stress can be reduced to less than the material yield stress, thus leaving only a recoverable viscoelastic deformation. Lastly, if the maximum viscoelastic deformation is small relative to the compact radius, then a suitable constitutive equation relating the instantaneous stress to the compact deformation is the Hertzian spring-dashpot (HSD) model. The elastic stress in the HSD model is given by:

$$F_{\text{elastic}} = K\delta^{32} \tag{3}$$

Here, K is related to the modulus of the compact, E_1, the modulus of the planar surface, E_2, the Poisson ratio of the compact, ν_1, and the Poisson ratio of the planar surface, ν_2, by:

$$K = \frac{\frac{4\sqrt{R}}{3}}{\frac{1-\nu_1^2}{E_1} + \frac{1-\nu_2^2}{E_2}} \tag{4}$$

Tsuji demonstrated that the expression for the dissipative force determines the dependence of the coefficient of restitution (COR) on the impact velocity [19]. As will be shown in Section 4, the COR for the compacts in this work are within experimental error of being independent of the impact velocity. An expression for a dissipative force that is independent of impact velocity is given by Eqs. (5) and (6) [17,19].

$$F_{\text{dissipative}} = \alpha(\epsilon)\sqrt{mK}\delta^{14}\dot{\delta} \tag{5}$$

Here, α is a function of the COR, ϵ:

$$\alpha(\epsilon) = \frac{-\sqrt{5}ln\epsilon}{\sqrt{ln^2\epsilon + \pi^2}} \tag{6}$$

And the coefficient of restitution is defined in terms of compact deformation as:

$$\epsilon \equiv -\frac{\dot{\delta}(\tau)}{\dot{\delta}(0)} \tag{7}$$

Where, τ is defined as the duration of the impact, which begins at time zero. Lastly, the gravitational force is:

$$F_{\text{gravity}} = -mg \tag{8}$$

Where g is the gravitational constant. Substituting the forces into the equation of motion gives:

$$m\ddot{\delta} - \alpha(\epsilon)\sqrt{mK}\delta^{14}\dot{\delta} - K\delta^{32} = mg \tag{9}$$

The 2nd order non-linear differential equation is solved with the following initial conditions to determine the compact deformation depth as a function of time during the impact.

$$\delta(t=0) = 0\ ;\ \frac{\mathrm{d}\delta}{\mathrm{d}t} = \sqrt{2gh} \tag{10}$$

Once the time dependent deformation is known, the impact force between the compact and the planar surface can be calculated, and compared to the measured force. The measured force is, by Newton's third law, collinear and equal in magnitude but opposite in direction to the force exerted by the load cell onto the compact. The only force imposed by the load cell upon the compact is the elastic contact force. Thus,

$$F_{\text{load cell}}(t) = -F_{\text{elastic}}(\delta(t); E_1, \nu_1) \tag{11}$$

The Young's elastic modulus and Poisson ratio are determined from fitting the measured load cell force with the theoretical elastic force by adjusting E_1 and ν_1. Note that the value for the compact COR required in the calculation of the dissipative force is not arbitrary, as it is explicitly defined by Eq. (7). One procedure to account for the coupled equations is to impose a self-consistency restriction, which can be accomplished by iteratively replacing the COR used in Eq. (6) with an updated COR value calculated by Eq. (7). The iterative procedure for the COR value requires additional computations that can substantially slow the fitting process. An alternative approach, as used in this work, is to calculate the COR from the measured load cell force by integrating the equation of motion over the total impact time.

$$\begin{aligned}\int_{mv_\mathrm{i}}^{mv_\mathrm{f}} \mathrm{d}(mv) &= mv_i\left[\frac{v_\mathrm{f}}{v_\mathrm{i}} - 1\right] \\ &= mv_i(\epsilon - 1) \\ &= \int_0^\tau F_{\text{loadcell}}(t)\mathrm{d}t\end{aligned} \tag{12}$$

Here, v_i and v_f are the impact and the rebound velocities of the compact, respectively, where the impact velocity is equal to $\sqrt{2gh}$. The calculation of the coefficient of restitution from the integrated load cell force ensures a physically tangible value and reduces the fitting process time, which is desirable for an in-process technique.