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A Practical Framework Toward Prediction of Breaking Force and Disintegration of Tablet Formulations Using Machine Learning Tools

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ABSTRACT

Enabling the paradigm of quality by design requires the ability to quantitatively correlate material properties and process variables to measureable product performance attributes. Conventional, quality-by-test methods for determining tablet breaking force and disintegration time usually involve destructive tests, which consume significant amount of time and labor and provide limited information. Recent advances in material characterization, statistical analysis, and machine learning have provided multiple tools that have the potential to develop nondestructive, fast, and accurate approaches in drug product development. In this work, a methodology to predict the breaking force and disintegration time of tablet formulations using nondestructive ultrasonics and machine learning tools was developed. The input variables to the model include intrinsic properties of formulation and extrinsic process variables influencing the tablet during manufacturing. The model has been applied to predict breaking force and disintegration time using small quantities of active pharmaceutical ingredient and prototype formulation designs. The novel approach presented is a step forward toward rational design of a robust drug product based on insight into the performance of common materials during formulation and process development. It may also help expedite drug product development timeline and reduce active pharmaceutical ingredient usage while improving efficiency of the overall process.

Introduction

The ever-expanding choices of drug delivery systems continue to be dominated by the solid dosage delivery in the form of tablets. A priori design of a tablet formulation for optimal performance requires a strategy for thorough understanding of the material properties and process conditions. Such an approach needs to be supported by a cascade of unit operation models and predictive technologies that quantitatively tie input material or process conditions to output performance characteristics (e.g., tablet breaking force, disintegration, dissolution, content uniformity, etc.) to generate or establish the necessary closure conditions to enable an inherently iterative design methodology.

The ability to quantitatively link formulation properties and process conditions to tablet breaking force and disintegration time provides the opportunity for developing design strategies for drug product development and process variables to meet target performance attributes, and thus advancing the quality-by-design (QbD) paradigm. From formulation and process science perspectives, the way that a tablet formulation is designed and manufactured may have profound effects on its physical properties such as tablet breaking force, disintegration, and stability.[1] These properties, in turn, have significant effects on the dissolution and bioavailability of tablet formulations.[2]

Tablet breaking force is relevant to ensuring dosage form robustness during manufacture (e.g., during coating) and during shipping and handling. It is primarily determined by the bonding mechanisms in effect and the development of significant, true areas of contact (e.g., surface area over which attractive force between particles is significant).[3] Tablet breaking force can be quantified by measuring the maximum stress, either compressive or tensile, that a tablet can sustain. A commonly used destructive test is to place tablets between 2 platens and measure the force necessary to fracture the tablets. Tablet breaking force, as determined by this test, is sometimes called “hardness,” although a more precise term is “breaking force.”

On the other hand, another factor that affects the performance of tablet formulations is the disintegration time. The disintegration of

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Table 1
Summary of Materials Used in This Study

Blend Number	Formulation	Quant.	Blend Number	Formulation	Quant.
Blend-1 (direct compression)	MCC 65% Lactose 31% Croscarmellose Na 3% Magnesium stearate 1%	321	Blend-2 (direct compression)	MCC 48% Lactose 48% Croscarmellose Na 3% Magnesium stearate 1%	252
Blend-3 (direct compression)	MCC 65%, 49.5%, 34% Lactose 34%, 49.5%, 65% Magnesium stearate 1%	264	Blend-4 (direct compression)	MCC 61% Lactose 30% Croscarmellose Na 3% PVP 5% Magnesium stearate 1%	40
Blend-5 (direct compression)	MCC 56% Lactose 30% Croscarmellose Na 3% PVP 10% Magnesium stearate 1%	40	Blend-6 (direct compression)	MCC 51% Lactose 25% Croscarmellose Na 3% PVP 20% Magnesium stearate 1%	40
Blend-7 (direct compression)	MCC 46% Lactose 20% Croscarmellose Na 3% PVP 30% Magnesium stearate 1%	40	Blend-8 (direct compression)	Ibuprofen 10% MCC 29% Lactose 60% Magnesium stearate 1%	18
Blend-9 (direct compression)	Ibuprofen 10% MCC 60% Lactose 29% Magnesium stearate 1%	18	Blend-10 (direct compression)	Ibuprofen 10% MCC 44.5% Lactose 44.5% Magnesium stearate 1%	18
Blend-11 (direct compression)	Ibuprofen 20% MCC 39.5% Lactose 39.5% Magnesium stearate 1%	18	Blend-12 (direct compression)	Ibuprofen 20% MCC 26.67% Lactose 52.33% Magnesium stearate 1%	18
Blend-13 (direct compression)	Ibuprofen 20% MCC 52.33% Lactose 26.67% Magnesium stearate 1%	18	Blend-14 (direct compression)	Ibuprofen 30% MCC 46.67% Lactose 22.33% Magnesium stearate 1%	12
Blend-15 (direct compression)	Ibuprofen 30% MCC 34.5% Lactose 34.5% Magnesium stearate 1%	18	Blend-16 (direct compression)	Ibuprofen 30% MCC 22.33% Lactose 46.67% Magnesium stearate 1%	18
Blend-17 (direct compression)	APAP 30% MCC 46.67% Lactose 22.33% Magnesium stearate 1%	9	Blend-18 (direct compression)	APAP 50% MCC 33.33% Lactose 15.67% Magnesium stearate 1%	9
Blend-19 (roller compaction)	Product A	90	Blend-20 (direct compression)	APAP 20% Lactose 43% MCC 30% Croscarmellose Na 3% Povidone 3% Magnesium stearate 1%	120
Blend-21 (direct compression)	APAP 20% Lactose 36% MCC 30% Croscarmellose Na 3% Povidone 10% Magnesium stearate 1%	120	Blend-22 (direct compression)	APAP 10% MCC 44.5% Lactose 44.5% Magnesium stearate 1%	18
Blend-23 (direct compression)	APAP 10% MCC 60% Lactose 29% Magnesium stearate 1%	18	Blend-24 (direct compression)	APAP 20% MCC 39.5% Lactose 39.5% Magnesium stearate 1%	18
Blend-25 (direct compression)	APAP 10% MCC 29% Lactose 60% Magnesium stearate 1%	18	Blend-26 (direct compression)	APAP 20% MCC 26.67% Lactose 52.33% Magnesium stearate 1%	18
Blend-27 (direct compression)	APAP 20% MCC 52.33% Lactose 26.67% Magnesium stearate 1%	18	Blend-28 (fluid bed granulation)	Product B	15
Blend-29 (fluid bed granulation)	Product C	15	Blend-30 (fluid bed granulation)	Product D	15
Blend-31 (high-shear wet granulation)	Product E	15	Blend-32 (high-shear wet granulation)	Product F	15
Blend-33 (direct compression)	MCC 31% Lactose 65% Croscarmellose Na 3% Magnesium stearate 1%	12	Blend-34 (direct compression)	APAP 30% MCC 22.33% Lactose 46.67% Magnesium stearate 1%	18
Total					1720

tablets refers to the disaggregation process of compressed particles in liquid before dissolution happens. The duration, known as "disintegration time," can be quantified with destructive tests performed in an isothermal bath. Although different pharmacopoeia specify distinct apparatus for tests, the most generic form consists of tubular containers which move vertically and bidirectionally in the