Quantitative Correlation of the Effect of Process Conditions on the Capping Tendencies of Tablet Formulations

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ABSTRACT: Capping is a mechanical defect in tablet formulation and manufacture. Understanding what influences tablet capping in terms of process variables and formulation properties and developing specialized techniques to correlate these variables with mechanical failures are practical interests of the pharmaceutical industry. Tablet compression emulator was used to rank order capping tendencies of a diverse sample set. The compression forces of 5–25 kN were used to compress round, beveled edge, and oval shape tablets. Compression speeds of 25, 40, and 80 rpm were chosen as representative ranges for bench-to-manufacturing-scale processing. Tablets were tested by in-house developed nondestructive ultrasonic method. The measurements revealed that elastic modulus vary with different testing orientations that indicated elastic modulus anisotropy in tablets. It was shown that altering process conditions such as tooling, compression force, and compression speed significantly impact the capping tendencies of formulations. A systematic approach has been applied to develop a predictive tool to assess capping tendencies of formulations. The developed tool is fast, material sparing, and has potential to flag the risk of manufacturability issues and provide insight into the performance of formulations during early development. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1652–1663, 2014

Keywords: tablet capping; compression; nondestructive ultrasonic testing; materials characterization; anisotropic properties; Material Science; mechanical properties; powder technology; tableting

INTRODUCTION

As a very effective and economic means of drug delivery, powder compaction is used extensively in pharmaceutical industry to convert drugs into metered solid dosage forms. Successful compact formation depends on the ability of the particles to deform and form interparticulate bonds during compression in the die and the ability of these bonds to withstand elastic expansion during decompression and ejection phases from the die. The behavior of the powder particles during compression is governed by factors such as pressure (i.e., stress), the amount of deformation (i.e., strain), and the rate of deformation (i.e., strain rate). During compression process, a blend of powders/granules containing active pharmaceutical ingredient(s) [API(s)] and excipients is compressed into tablets on a high-speed rotary press. The blend is confined radially by a rigid die while being compressed axially with punches. The process conditions, compression deformation characteristics (i.e., elastic, viscoelastic, visco-plastic, plastic deformation), material properties of powders and ambient conditions of temperature and humidity determine physical and mechanical properties of final tablets. During this process, as the pressure increases, volume reduction is achieved by initially elastic deformation and then plastic deformation and/or fragmentation of the particles. The tablet formation continues during the decompression phase. During unloading phase, the stored elastic strain that is gained during compression will be released (i.e., stress/strain relaxation). This process creates heterogeneous internal tablet structure upon removal of the upper punch that may lead to failure modes such as capping and lamination and consequently decreases the overall integrity of the tablet.[1–8] Capping is the separation of the top or bottom curvature part of the tablet (i.e., cup depth region) from the tablet body either partially or completely during ejection, subsequent handling, or physical testing. Tablet capping, as compact emerges from the die or during physical testing, is one of the common tableting problems that may occur during processing, handling, packaging, shipping, and storage.

Although it was first characterized in 1954[9] and has been studied ever since, the causes of tablet capping have yet to be fully understood. Various theories have been proposed through the years in order to explain this complex phenomenon. Some reported root causes of tablet capping include fracture of the interparticulate bonding rather than the production of adhesive forces that have insufficient strength during compression,[10] excessive elastic recovery and high compression speed,[11] anisotropic mechanical properties,[8] air entrapment,[12] nonuniform density and stress distribution in the tablet,[2] elastic component of brittle materials that in turn causes a reduction in the interparticulate bonding during unloading phase,[12–14] volume reduction mechanism,[15] and die-wall pressure that causes internal shear stresses in the tablet.[16] One may mitigate capping issues by adjusting formulation and process variables. From the formulation perspective, increasing the binder concentration, using plastically deforming materials and reducing the percentage of fine particles within the formulation are some of the practical remedies to reduce capping occurrence.[9,11,17,18] From the process science perspective, practical remedies may include reducing capping by changing tooling shape,[16] decreasing punch tolerance (i.e., the air gap between punch tip and the die-wall),[14] using low compression pressures,[10] and slowing the turret speed (i.e., increasing the dwell time).[12] However, these approaches are often taken on

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a "trial-and-error" basis after capping issues are already observed during manufacturing.

A priori design of tablet formulations for optimal performance requires a strategy for selecting input material properties, process conditions, and advanced characterization methods. Such an approach needs to be supported by quantitative correlation of input materials/process conditions to output performance characteristics, providing in this manner the necessary closure conditions to enable a strategy for *a priori* drug product and process design. It will be greatly desired if one can understand what influences the stress state and mechanical properties of a tablet, and develop advanced material profiling tools and performance maps to predict capping tendency. This helps flag risk early on, reduce API consumption and cost and facilitate the drug product development timelines. It is a step forward toward rational design of a robust drug product. The goal of this study is to quantitatively predict the capping tendency of various formulations by characterizing a representative design space for bench-to-manufacturing-scale processing. Spanning a large design space provides a multidimensional view of the particular blend or class of blends, allowing for the development of a model for regions where factor combinations produce the highest and lowest quality tablets. In such a system, it would be possible to select precise levels of process variables (i.e., compression speed, compression force, and tooling shape) that would operate within the acceptable, capping-free space, and achieve quality tablets in a predictable manner.

EXPERIMENTAL

Materials

In this study, a diverse set of materials were used. The same formulation blends were also investigated in the previous publication for the proposed proof-of-concept approach.[2] Microcrystalline cellulose (MCC) or Avicel PH102 NF (FMC Biopolymer, Newark, Delaware), lactose monohydrate PhEur/USPNF/JP, or Tablettose 80 (Mutchler Inc., Meggle AG, Germany), ascorbic acid powder USP/FCC (Fisher Scientific, Pittsburgh, Pennsylvania), acetaminophen or APAP (Acros Organics, part of Thermo Fisher Scientific, Fair Lawn, New Jersey), and magnesium stearate (MgSt) (Hyqual®-N.F grade; Mallinkrodt, Covidien, St. Louis, Missouri) were employed as the test materials and the lubricant, respectively.[2] APAP is well known for its capping tendency.[18] MCC is often used as a filler and binding agent in tablet formulations because of its excellent compression properties.[17] Lactose is a common direct compression filler selected primarily because of its excellent flow properties and moderate compression properties.[17,19] Ascorbic acid was selected because of its poor compactability.[17] Final compression blends of commercial products (coded as 1 through 10) were received from Boehringer-Ingelheim's (BI's) manufacturing facilities worldwide. In this study, all the formulations tested were representing a wide range of material characteristics (i.e., from ductile to viscoelastic to brittle).

Methods

Blend Preparation

Before mixing, 0.5% (w/w) MgSt as a lubricant to powder was added to the single, binary, and tertiary systems, unless otherwise noted (Table 1).[2] Each powder system was manufactured with different fractions of constituent components by mixing powders in a Turbula T2F Shaker Mixer (Mashinenfabric®; Willy A. Bachofen AG, Basel, Switzerland) for 4 min at 32 rpm.[2] API/excipient ratios were established based on prior capping observations with these materials. The true density values of all tested materials were measured using a helium gas displacement pycnometer (Type AccuPyc 1330; Micrometics®, Bedfordshire, UK). Prior to testing, all materials used in this study were placed in desiccators and equilibrated overnight over saturated solution of potassium carbonate that gives 43% relative humidity (RH). Loss on drying was tested (after overnight exposure to 43% RH) using a moisture analyzer (HR83; Mettler-Toledo AG, Greifensee, Switzerland), by heating samples to 105°C (i.e., standard drying mode).

Table 1. True Densities and Loss on Drying (LOD) Values of Blends

Material	True Density (g/cm^3)	LOD (%)
Tablettose 80—unlubricated	1.5406	0.15
Tablettose 80—lubricated	1.5406	0.15
MCC PH102	1.5656	4.67
Acetominophen	1.2989	0.19
Ascorbic acid	1.6981	0.09
Binary: APAP/Tablettose 80 0.5% MgSt		
APAP/Tablettose 80 1/98.5	1.5361	0.26
APAP/Tablettose 80 3/96.5	1.5304	0.23
APAP/Tablettose 80 5/94.5	1.5265	0.23
APAP/Tablettose 80 20/79.5	1.4888	0.18
Binary: APAP/MCC PH102 0.5% MgSt		
APAP/MCC PH102 20/79.5	1.5107	3.32
Binary: Ascorbic acid/Tablettose 80 0.5% MgSt		
Ascorbic/Tablettose 80 5/94.5	1.5463	0.15
Ascorbic/Tablettose 80 10/89.5	1.5520	0.15
Ascorbic/Tablettose 80 20/79.5	1.5654	0.12
Binary: Ascorbic acid/MCC PH102 0.5% MgSt		
Ascorbic/MCC PH102 40/59.5	1.5895	3.84
Ascorbic/MCC PH102 60/39.5	1.6126	2.95
Ascorbic/MCC PH102 80/19.5	1.6420	2.01
Tertiary Blends		
APAP/MCC PH102/Tablettose 80 20/39.5/40	1.5127	1.97
Ascorbic/MCC PH102/Tablettose 80 40/39.5/20	1.6231	1.85
Final compression blends of BI commercial products		
Product-1	1.5085	5.36
Product-2	1.7355	3.82
Product-3	1.7620	3.51
Product-4	1.3165	1.13
Product-5	1.4119	1.04
Product-6	1.4017	1.41
Product-7	1.4089	1.87
Product-8	1.5139	1.71
Product-9	1.4224	5.90
Product-10	1.5315	2.53

Tablet Compression

All tablets were compacted by the Presster™ (Software Version 4.2.0; Metropolitan Computing Corporation, East Hanover, New Jersey) simulating FETTE P1200 with 30 stations in a temperature controlled room held at 22 ± 1°C and 63 ± 2% RH. Presster™ was calibrated weekly and the calibration verified before the compression of every blend. Tooling is one of the