Development of New Shaped Punch to Predict Scale-up Issue in Tableting Process

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ABSTRACT: Scale-up issues in the tableting process, such as capping, sticking, or differences in tablet thickness, are often observed at the commercial production scale. A new shaped punch, named the size adjusted for scale-up (SAS) punch, was created to estimate scale-up issues seen between laboratory scale and commercial scale tableting processes. The SAS punch's head shape was designed to replicate the total compression time of a laboratory tableting machine to that of a commercial tableting machine. Three different lubricated blends were compressed into tablets using a laboratory tableting machine equipped with SAS punches, and any differences in tablet thickness or capping phenomenon were observed. It was found that the new shaped punch could be used to replicate scale-up issues observed in the commercial tableting machine. The SAS punch was shown to be a useful tool to estimate scale-up issues in the tableting process. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:235–240, 2014

Keywords: tableting; compression; compaction; solid dosage form; mathematical model; punch; capping; hardness; thickness

INTRODUCTION

In the scale-up process of pharmaceutical products, it is sometimes observed that differences in batch size have a significant impact on physical properties of a drug product. The main root causes of these issues have traditionally been attributed to processes such as granulation, blending, and lubrication; however, the tableting process has also been considered one of the critical processes. For the granulation process, a number of studies have been widely investigated to clarify the granulation conditions.[1,2] Recently, several parameters of the granulation process at mini-scale production were selected to predict physical properties of granules.[3] For the tableting process, there is usually no issue during the early formulation development stage, however, unexpected tableting problems, such as sticking, capping, or lamination, have been observed at the commercial manufacturing stage. When the deformation mechanism and elastic recovery during compression that influence tablet capping[4] is often seen, formulation change is a better way to eliminate tablet capping phenomenon rather than optimization of the tableting conditions. Late stage formulation changes are very difficult and costly in practice because the various pivotal studies required to support such a change (e.g., clinical study, stability study, or bioequivalence study) have already been completed. In some cases, it is possible to introduce or change the plating materials on the punches to resolve the capping or sticking phenomenon[5] without the need for additional studies. In either case, the development program may be delayed by the considerable time needed to solve such problems. Simulations have been attempted to model the results seen at laboratory scale onto commercial scale. A compaction simulator[6] and a fuzzy model[7] were applied to estimate capping tendency; however, these tools do not currently allow accurate prediction and simulation of scale-up problems.

In addition, tablet thickness changes depending on the size of tableting machine used are well known in the industry. The tablet thickness observed at the full scale is sometimes thicker than that at 1/10th scale. If the tablet thickness from the 1/10th scale production is filed as a specification in a submission document, it can be difficult to change the specification after approval of the product. In such a case, compression force on the commercial machine would likely be increased to achieve the target thickness, with a potential adverse impact on the tablet dissolution or resulting in damage to the tooling such as chipping. Moreover, changes in the tablet thickness may also have adverse impacts in downstream packaging activities such as blister packaging by blocking tablet feeding mechanisms. Therefore, it is important to be able to predict and control the tablet thickness in the commercial manufacturing process.

For tableting process, scale-up issue comes from differences in the size of tableting machine.[8] The radius of the turret on a typical laboratory tableting machine is smaller than that of a commercial tableting machine. This means that both the consolidation time and dwell time of the laboratory machine will be longer than on a typical commercial machine, when the turret rotation speed is the same. On a rotary tablet press, the force–time curves are segmented into three distinct phases, the consolidation phase, the dwell phase, and the decompression phase.[9] The difference in the total compression time (sum of consolidation and dwell times) between a laboratory and a commercial tableting machine is considered one of the main root causes of scale-up issues in tableting processes. It has been reported when tableting troubles were observed in the commercial production stage, changes to the punch head by elongating the flat can be used to prolong the dwell time.[10] This means the difference between the dwell times on a laboratory and commercial tableting machine can be minimized to reduce tableting issues observed at the commercial manufacturing stage. It is presumed that scale-up issues could also be reduced if the

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differences in total compression time between the laboratory and commercial tableting machine could be minimized as well. The total compression time can be calculated from the calculation of punch velocity.[11–13]

In this article, a new shaped punch was designed and created, called the size adjusted for scale-up (SAS) punch. When used in conjunction with a laboratory scale tablet press, the SAS punch was shown to simulate the tablet properties produced by a commercial tablet press equipped with conventional punches. This has been confirmed by compressing three different drug product formulations using the laboratory scale press with SAS punches design and comparing the results for the same products on a commercial scale tablet press with conventional punches.

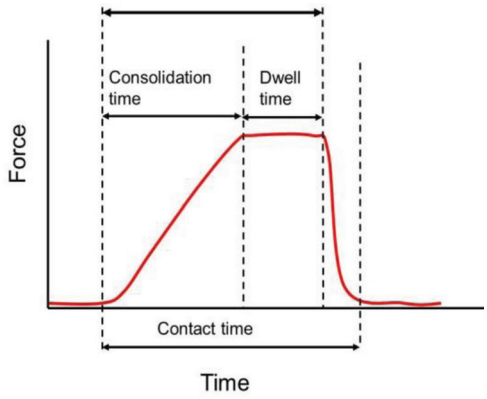

Figure 1. Events during compression process.

MATERIALS AND METHODS

Materials

Three different lubricated product blends A, B, and C, were supplied by Eisai Company Ltd. (Kawashima or Misato factory). Blend A contains 1 mg of potassium warfarin, anticoagulant in 144 mg of total blend. Blend B contains 10 mg of sodium rabeprazole, a proton pump inhibitor in 120 mg of total blend. Blend C contains 100 mg of new anticoagulant drug substance in 300 mg of total blend. Granules of each blend were manufactured by a wet granulation method, and each granule was lubricated with magnesium stearate.

Preparation of Tablets

The lubricated blends were compressed into tablets under various compression forces using a laboratory tablet press (15 stations, Hata Iron Works Company, Ltd., Kyoto, Japan) and one of three commercial tablet presses (blend A: 38 stations; Hata Iron Works Company, Ltd., blend B: 45 stations; Hata Iron Works Company, Ltd., blend C: 20 stations; Fette P1200, Fette Compacting GmbH, Schwarzenbek, Germany). Lubricated blend A was compressed into flat face tablets with a tablet diameter of 7.5 mm and a target weight of 144 mg. Lubricated blend B was compressed into biconvex tablets with a tablet diameter of 6.5 mm and a target weight of 120 mg. Lubricated blend C was compressed into biconvex tablets with a tablet diameter of 9.5 mm and a target weight of 300 mg.

Lubricated blends A and B were compressed into tablets using the same head shape for both the upper and lower punches (either conventional or SAS). Lubricated blend C was compressed using a combination SAS and conventional punches in the upper and lower positions and shown to have an impact on capping tendency.

During the tableting process, the tablet weight was periodically monitored using a digital balance and the mean tablet weight was controlled at a targeted ±1 mg.

Punch Manufacturer

Conventional and SAS punch (Mark II type) was supplied from Mori Machinery Company, Ltd., (Okayama, Japan) and was fabricated using a nickel–chrome–molybdenum steel. The steel was turned on a lathe to the rough dimensions desired prior to any heat treatment. After heat treatment, the steel was returned to the lathe and precision turned before the final manufacturing using a computer-numerically controlled milling and drilling machine.

Measuring Method

Thickness and hardness of 20 tablets were measured by micrometer (Mitutoyo Company; Sakado, Takatsu-Ku, Kawasaki-Shi, Kanagawa 213-8533, Japan) and hardness tester (Fujiwara Seisakusho Company; Nishigahara Kita-Ku Tokyo 114-0024, Japan), respectively. The mean value for each parameter was calculated. The capping tendency was evaluated by a manual drop tests that involved dropping 20 tablets from a 2 m height onto a flat marble surface. After being dropped 10 times, the appearance of each tablet was inspected for any differences such as capped, tipped, or cracked tablets. The drop test was performed triplicated.

Preparation of SAS Punch

Total compression time[14] is expressed as the sum of the consolidation time and the dwell time as shown in Figure 1. The consolidation time is a measure of the time between initial punch contact with the compression roller and observation of the maximum force. The consolidation time is related to the peripheral speed of the turret. The dwell time is a measure of the time the punch head flats are in direct contact with the compression roller. This is the time when the maximum pressure is applied to the blend. The dwell time is relative to the peripheral speed of the turret and the diameter of the punch head flats. Because a tablet press for commercial production is larger than that for laboratory production, the consolidation time and the dwell time of tableting machine for the commercial production are shorter than those of tablet press for laboratory production. Figure 2 represents the relationship between punch, compression roller, and the die turret of a rotary process, viewed both from the side and from above. The lightly shaded area indicates the punch head area, and the darker shaded area indicates the area of the punch head flat. As a punch rotates with a turret, the punch is raised and lowered by punch head contact with the cam track.

The consolidation time is the time that a punch moves the horizontal distance (d_2) between the vertical center lines at the compression roller and the contact point of the compression roller and the punch as shown in Figure 2. The angular velocity of the turret over a period of 60 s is expressed as $2\pi N$, where, N is rotation speed (rpm) of turret. On the other hand, the consolidation time is the time required for the punch to move by the horizontal distance (d_2). The angular velocity each arcminute for d_2 is then expressed as $\sin^{-1}(d2/R)$. Therefore, the

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