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Influence of disintegrants in different substrate physical form on dimensional recovery of multi-component tablet

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ABSTRACT

This study investigated the influence of different disintegrants, present in different substrate physical forms, on dimensional recovery of multi-component tablets prepared at different compression pressures. Formulations containing model drug, metformin, (10%, w/w), different disintegrants (10%, w/w), and lactose (80%, w/w) were compressed directly or after granulation using polyvinyl pyrrolidone (1%, w/w) as binder, into tablets (350 mg, 10 mm diameter) at 150, 200, and 250 N/mm^2 compression pressures. Tablets were characterized for immediate dimensional recovery (IR) after ejection from the die, latent dimensional recovery (LR) over 24 h, tensile strength, and disintegration. The IR was predominantly contributed by crystalline components whereas LR was brought about by polymeric materials. With increased compression pressure, higher degree of plastic deformation of the polymeric disintegrants resulted in tablet with lower LR and higher tensile strength. Presence of polyvinyl pyrrolidone in the granules contributed considerably to plastic deformation, and the tablets produced had lower LR, higher tensile strength, and longer disintegration time. This study indicated that use of granules as the feed substrate physical form and a prudent selection of components may enable the coating of resultant tablets immediately after compression without the risk of coat damage due to LR.

1. Introduction

Dimensional recovery of a compressed tablet is defined as the change in tablet dimensions after unloading of compression pressure (Doelker, 1993). Upon release of the pressure, the tablet exhibits an instantaneous immediate dimensional recovery (IR), followed by a gradual time-dependent latent dimensional recovery (LR) during storage (Haware et al., 2010). The IR is generally believed to be one of the main contributors to tablet capping or lamination (Maarschalk et al., 1996) whereas the LR is better associated with coat damage of the subsequently coated tablet (Marshall, 1999). Hence, prior to coating, compressed tablets are aged for a period of time, typically 24 h, to allow completion of the LR event in order to avoid coat damage. Therefore, LR is one of the constraints in the application of the coating on the tablets immediately after compaction. Dimensional recovery has been considered as inevitable in tablets after compression, but little research has been directed at studying dimensional recovery. However, if the extent and time taken for dimensional recovery can be reduced by better understanding of its attribute, compressed tablets could be coated soon after production without the need of an aging period. This enables implementation of continuous manufacturing to resolve the pressing need in the pharmaceutical industry for a more cost effective production. Achievement of the above mentioned purpose requires a prudent selection of components in the feed substrate, and a good understanding of the feed substrate and their response to different tabletting process parameters.

Investigations on the dimensional recovery of different pharmaceutical powders, such as active pharmaceutical ingredients (APIs), disintegrants and fillers have been variously reported (Maarschalk et al., 1997; Řehula and Adámek, 2008; Picker, 2001; Mohammed et al., 2005; Haware et al., 2010; Pilpel et al., 1992). Usually, the APIs and fillers are crystalline materials and exhibit high and fast IR but low LR, whereas the disintegrants, which are usually polymeric in nature, undergo mainly viscoelastic deformation and exhibit relatively higher LR. Pharmaceutical tablets are commonly prepared from a multi-component mixture comprising of API, and one or multiple filler, binders, disintegrant, lubricant, and other substances such as

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glidants. It was reported that presence of certain components, even in low concentration, could influence densification behavior by affecting the yield pressure of the mixture (Ilkka and Paronen, 1993; Bouvard, 2000) and thereby the matrix structure, such as pore size and size distribution (Bockstiegel, 1967) as well as the mechanical properties of the tablet (Mattsson and Nyström, 2000; Vromans and Lerk, 1988). For the reported studies on tablet recovery, most were conducted on single component tablets and only a few studies investigated tablets containing multi-component mixture (Pilpel et al., 1992; Nokhodchi and Rubinstein, 1998; Picker, 1999). Studies on the dimensional recovery of tablets prepared from the binary powder mixtures containing ibuprofen and hydroxypropylmethyl cellulose (Nokhodchi and Rubinstein, 1998), and carrageenan and microcrystalline cellulose (Picker, 1999) showed that there was no direct relationship between the dimensional recovery of the tablets prepared from a binary mixture and those from the individual components. As mentioned earlier, the API, disintegrant and filler are basic components of a tablet formulation and most fillers and APIs show high IR and low LR but the opposite is observed for disintegrants. Therefore, it is highly desirable to investigate the dimensional recovery of tablets containing all basic components. In addition, the influence of feed substrate physical form on the dimensional recovery of tablet has also not been well discussed. In almost all of the reported studies, tablets were prepared using unprocessed powders or powder mixtures. There remains a paucity of information on the influence of the granulation process on dimensional recovery of tablets.

This study aimed to evaluate the influence of different disintegrants, present as different substrate physical forms, on dimensional recovery of tablets prepared using different compression pressures from multi-component formulations. Six different disintegrants were chosen, and tablets were prepared by either direct compression of powder mixtures (metformin 10%, w/w, disintegrant 10%, w/w, and lactose 80%, w/w) or compression from granules prepared by high shear granulation from the powder mixture using 1%, w/w (calculated based on powder mixture weight) polyvinyl pyrrolidone as wet binder. Tablets were also prepared by replacing disintegrant with lactose in the formulation, compressed directly or after granulation in a similar way, to serve as the base line control tablets (STD) to evaluate the influence of disintegrant on dimensional recovery of tablets.

2. Materials and methods

Croscarmellose sodium (CCS, median particle size 47.2 ± 0.1 μm, Ac-Di-Sol FMC BioPolymer, USA), low-substituted hydroxypropyl cellulose (LHPC, 58.3 ± 0.6 μm, LH-21, Shin-Etsu Chemical, Japan), partially pregelatinized starch (PGS, 76.4 ± 4.3 μm, Starch 1500, Colorcon, USA), sodium starch glycolate (SSG, 44.3 ± 0.4 μm, Primojel, DFE Pharma, The Netherlands), and cross-linked polyvinyl pyrrolidone (XCL, 97.5 ± 4.8 μm, Kollidon CL, BASF, Germany; XXL, 183.5 ± 5.7 μm, Polyplasdone XL, Ashland, USA; and XXLF, 93.8 ± 2.4 μm, sieved fraction of XXL) were used as disintegrants. Lactose (160.3 ± 2.6 μm, Spherolac 100; and 18.4 ± 0.1 μm, Granulac 200; Meggle, Germany) was used as filler, and metformin (216.3 ± 3.0 μm, Granules India, India) was the model API. For granulation, polyvinyl pyrrolidone (PVP, Kollidon 30, BASF, Germany) at 1%, w/w (based on dry powder weight) in distilled water was used as the moistening liquid. Magnesium stearate (M125, Productos Metallest, Spain) was the lubricant used.

2.1. Granulation

Metformin (200 g), disintegrant (200 g; for STD, disintegrant was replaced with Granulac 200), and Granulac 200 (1600 g) were placed in the bowl of a high shear granulator (UltimaPro 10L, GEA-Collette, Belgium) and dry mixed at 500 rpm for 2 min. The amounts of water used to prepare granules of different formulations were predicted using the rheological profiles of the corresponding powder mixtures on liquid addition in a mixer torque rheometer (Caleva Process Solutions, UK) by the method reported earlier (Sarkar et al., 2013). The amount of water used for granulation was 55% of W_{Tmax}, the amount required to achieve maximum torque. PVP (20 g) was dissolved in the calculated amount of water and delivered for wet massing over 5 min with the impeller and chopper rotating at 500 and 2700 rpm, respectively. Wet massing was continued for another 5 min, and the resultant granules were passed through a cone mill (Comil U5, Quadro Engineering, Canada) fitted with a square–hole screen of aperture size 4750 μm. Granules were then dried in a fluid bed drier (Strea-1, GEA-Aeromatic,Switzerland) at 45 °C until the product temperature reached 40 °C. The dried granules were subsequently de-agglomerated by cone milling again through a grater screen of aperture size 1016 μm. Median size of granules prepared from STD formulation was 164 ± 1 μm, and formulations containing PGS, SSG, CCS, LHPC, XCL, and XXL were 163 ± 4, 173 ± 4,134 ± 2, 146 ± 8, 211 ± 1, and 181 ± 1 μm, respectively.

2.2. Tablet compression

Cylindrical round tablets (350 mg) were prepared using 10 mm flat-faced bevel-edged punches on a rotary tablet press (Courtoy R190FT, GEA Pharma Systems, Belgium) at 150, 200, and 250 N/mm^2 compression pressures. Feed substrate was either powder mixtures consisting of Spherolac 100 (80%, w/w), metformin (10%, w/w), and disintegrant (10%, w/w; for STD, disintegrant was replaced with Granulac 200) or granules prepared by high shear granulation. Tabletting feed substrate was mixed with lubricant, 1%, w/w magnesium stearate prior to tabletting.

2.3. Tablet characterization

Tablets were characterized for their dimensional recovery, tensile strength and disintegration.

2.3.1. Dimensional recovery measurement

Tablet dimensional in both axial and radial directions were measured continuously in a controlled environment of 25 °C and 50% relative humidity using calibrated laser displacement sensors (OptoNCDT 1700-20, Micro-Epsilon, Germany) fitted in an instrument comprising a turntable (Fig. 1), as described by Cahyadi et al. (2012). These laser displacement sensors measure accurately the distances between the platforms and sensors. Hence, tablet dimensions in the axial and radial directions were determined from the differences between measurement tracings made with and without tablets loaded on the platforms. Immediately after compression, five tablets from each formulation were placed on five platforms of the turntable rotating at 1 rpm. A fully recovered lactose tablet, compressed using the same tablet press and tooling at least a month prior to experimentation, was placed on one platform of the turntable. It served as a control to assess the extent of fluctuation in the dimensions of measured tablet due to environmental factors. The dimensions of the tablets were recorded over 24 h, every minute during the first 2 h and