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Differential compaction behaviour of roller compacted granules of clopidogrel bisulphate polymorphs

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ABSTRACT

In the present work, in-die and out-of-die compaction behaviour of dry-granulated powders of clopidogrel bisulphate (CLP) polymorphs, form I and form II, was investigated using a fully instrumented rotary tablet press. Each polymorph was compacted at three different roller pressures [70.3 (S1), 105.5 (S2) and 140.6 (S3) kg f/cm^2], and obtained granules were characterized for their physico-mechanical properties. Compaction data were analyzed for out-of-die compressibility, tabletability and compactibility profiles, and in-die Heckel, Kawakita and Walker analysis. The roller compacted granules of both forms showed markedly different tabletting behaviour. Roller pressure exhibited a trend on compaction behaviour of form I granules, whereas, in case of form II, the effect was insignificant. Tabletability of the six granule batches follows the order; I_S1 > I_S2 > I_S3 > II_S1 ≈ II_S2 ≈ II_S3. In case of form I, the reduced tabletability of the granules compacted at higher roller pressure was attributed to the decreased compressibility and plastic deformation. This was confirmed by compressibility plot and various mathematical parameters derived from Heckel (Py), Kawakita (1/b) and Walker (W) equations. The reduced tabletability of form I granules was due to 'granule hardening' during roller compaction. On the other hand, insignificant effect of roller compaction on tabletting behaviour of form II granules was attributed to brittle fragmentation. The extensive fragmentation of granules offered new 'clean' surfaces and higher contact points that negated the effect of granule hardening.

1. Introduction

Quality by design (QbD) initiatives of US FDA require scientific understanding of critical material attributes and process parameters (Lawrence, 2008). Knowledge of the mechanical properties of the drug and excipients plays a crucial role in solid dosage form design and development. In pharmaceuticals, polymorphism offers a unique opportunity to study the effect of molecular level material properties on the mechanical behaviour of pharmaceutical materials. This is because of the constancy of chemical composition that eliminates the complexity caused by different molecular structures. Recently, we have reported the influence of molecular properties like crystal packing density, differential molecular packing, slip plane systems and thermodynamic properties on the compaction behaviour of pharmaceutical powders (Khomane and Bansal, 2013b,c; Khomane et al., 2012, 2013). Additionally, relative contribution of molecular and particulate properties towards tabletability has also been investigated (Khomane and Bansal, 2013a).

Tabletability of the studied polymorphic systems viz. clopidogrel bisulphate (CLP) form I and II (Khomane et al., 2012), ranitidine hydrochloride (RAN) form I and II (Khomane and Bansal, 2013b; Upadhyay et al., 2013), and indomethacin (IMC) α and γ-forms (Khomane et al., 2013), was found to be governed by compactibility rather than compressibility. Tabletability represents tensile strength under the effect of compaction pressure while compactibility and compressibility are measure of the interparticulate bonding strength and bonding area, respectively (Joiris et al., 1998; Sun 2011). It was observed that the polymorph showing greater compactibility (higher bonding strength) showed increased tabletability, despite poor compressibility and plastic deformation (lower bonding area). In case of RAN polymorphs, decrease in particle size increased the compressibility and plastic deformation of form II significantly. However, form I still showed greater tabletability by virtue of its greater interparticulate bonding strength (Khomane and Bansal, 2013a). Like particle size, roller compaction has also been reported to alter the compressibility and plastic deformation of the pharmaceutical powders (Kuntz et al., 2011; Patel et al., 2011, 2008; Sun and Himmelspach, 2006). Hence, it is interesting to study the effect of

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roller compaction on the overall compaction behaviour of a polymorphic pair.

The present study investigates the effect of roller compaction pressure on both, in-die and out-of-die, compaction behaviour of CLP polymorphs. In a previous report, form I showed greater tabletability over form II, despite poor compressibility and plastic deformation under the applied compaction pressure (Khomane et al., 2012). This counterintuitive behaviour was attributed to higher crystal packing density that conferred greater compactibility (interparticulate bonding strength) to the compact of form I.

Roller compaction was reported to reduce the tabletability (Patel et al., 2011; Sun and Himmelspach, 2006). The phenomenon was termed as 'loss of reworkability' or 'loss of tabletability'. This reduced tabletability of the compacted granules was ascribed to decreased compressibility and plastic deformation due to 'work hardening' or 'granule size enlargement'. However, roller compaction essentially does not influence the interparticulate bonding strength as it is governed by intermolecular interactions. Hence, in the present work, greater tabletability of form I over form II is expected by virtue of its higher interparticulate bonding strength. However, roller pressure may show markedly different trend on tabletability of the two polymorphs and need to be investigated. Hence, each polymorph was compacted at three different roller pressures [70.3 (S1), 105.5 (S2) and 140.6 (S3) kg f/cm^2], de-sized to granules and was compressed using a fully instrumented rotary tablet press. Compaction data were analyzed for compressibility, tabletability and compactibility profiles, and Heckel, Kawakita and Walker analysis.

2. Material and methods

2.1. Clopidogrel bisulphate polymorphs

Two polymorphs of CLP namely form I and form II were kindly gifted by Ind-Swift Laboratories Ltd. (India).

2.2. Powder X-ray diffraction (PXRD)

PXRD of 'as received' samples was recorded at room temperature on Bruker's D8 advance diffractometer (Bruker, Germany) with Cu Kα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter. Analysis was performed with a step size of 0.05° and step time of 5 s over an angular range of 3–40° 2θ. Obtained diffractograms were analyzed with DIFFRAC plus EVA (version 9.0) diffraction software.

2.3. Differential scanning calorimetry (DSC)

DSC analysis was performed using DSC, Model Q2000 (TA Instruments, USA) operating with Universal Analysis® software (version 4.5 A). About 2.5–3.0 mg of CLP was accurately weighted in crimped aluminum pans and subjected to the thermal scan of 40–220 °C at the heating rate of 10 °C min^{-1}. The dry nitrogen purge was maintained at 50 mL min^{-1}. Prior to analysis, calibration of the instrument was performed using high purity zinc (Zn) and indium (In).

2.4. Moisture content

Moisture content of 'as received' samples was determined by Karl Fischer (KF) titration (Metrohm 794 Basic Titrino, Switzerland). Instrument was calibrated with disodium tartrate dihydrate for the accuracy of moisture determination. Sample size of approximately 300 mg was utilized for the determination of moisture content (n = 3).

2.5. Roller compaction

Ribbons of both the polymorphs of CLP were prepared using a roller compactor (Clit Mini Roller Compactor, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India). The roll speed and the feeder speed were kept at 5 and 50 rpm, respectively. A hopper with a 2.5 L volume having bore diameter of 19 mm was used for charging the powder. Corrugated rolls of 100 mm in diameter and 25 mm in width were used for roller compaction. Different roll pressures, i.e. 70.3, 105.5 and 140.6 kg f/cm^2 were utilized for the preparation of ribbons. Large ribbons were manually broken into smaller pieces and subsequently passed through BSS # 16, and those retained on BSS # 20 were used for tablet compaction. The granules obtained after sieving from 70.3, 105.5 and 140.6 kg f/cm^2 roller compaction pressure were designated as batch S1, batch S2 and batch S3, respectively.

2.6. Granule size distribution

Similar granule size range (800–1200 μm) of the six batches was obtained by sieving. The D_{90} and D_{50} of each batch were determined by measuring diameter along the longest axis for at least 200 granules by optical microscopy (DMLP microscope, Leica Microsystems, Wetzlar, Germany).

2.7. Scanning electron microscopy (SEM)

Morphology of the granules obtained after sieving was studied using a scanning electron microscope (S-3400, Hitachi Ltd., Tokyo, Japan) operated at an excitation voltage of 15 kV. Granules were mounted onto steel stage using double sided adhesive tape and coated with gold using ion sputter (E-1010, Hitachi Ltd., Tokyo, Japan).

2.8. Apparent particle density and flow properties

The apparent particle density of both the polymorphs was determined in triplicate at 25 ± 2 °C/40 ± 5% RH by helium pycnometry (Pycno 30, Smart Instruments, India).

Bulk density was calculated by carefully adding accurately weighed (about 100 g) powder to 250 mL measuring cylinder. Corresponding volume was calculated to get the bulk density. Tapped density was calculated using USP tap density apparatus (Electrolab, Mumbai, India) as per USP II method. Flowability of the material was determined by calculating Hausner ratio (HR) and Carr's index.

2.9. Single particle fracture strength

The measurement of single particle nominal fracture strength of the compacted granules was performed using a texture analyzer (TA-XT2i, Stable Micro Systems, Surrey, UK) as described previously (Khomane and Bansal, 2013a; Patel et al., 2011, 2007, 2008). Briefly, all the experiments were performed using 5 kg load cell and 2 mm flat faced probe. The force–displacement and force–time measurements were obtained by employing a pre test speed of 0.4 mm/s, test speed of 0.2 mm/s (fracture speed) and post test speed of 0.6 mm/s. The data acquisition rate was 200 points per second using a fully integrated data acquisition and analysis software (Texture Expert, version 1.22, TA-XT2i, Stable Micro Systems, Surrey, UK). A stainless steel support was kept on platform to support the test particle. The probe was vertically moved down on single particle until it fractured. Nominal fracture strength of 25 randomly selected granules from each batch was individually measured at 25 ± 2 °C/30 ± 5% RH.