Journal of Pharmaceutical Sciences xxx (2016) 1-9

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Single-step Coprocessing of Cohesive Powder *via* Mechanical Dry Coating for Direct Tablet Compression

Li Qu [1], Peter J. Stewart [1], Karen P. Hapgood [2], Satu Lakio [3], David A.V. Morton [1,*], Qi (Tony) Zhou [4,*]

[1] *Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3055, Australia*
[2] *Department of Chemical Engineering, Monash University, Clayton, Victoria 3800, Australia*
[3] *AstraZeneca R&D, Pepparedsleden 1, 43183 Mölndal, Sweden*
[4] *Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, West Lafayette, Indiana 47907-2091*

ARTICLE INFO

Article history:
Received 22 March 2016
Revised 4 July 2016
Accepted 20 July 2016

Keywords:
fine cohesive powder
mechanical dry coating
flowability
direct compression
lubrication
dissolution

ABSTRACT

This study aims at testing the feasibility of a single-step coating process to produce a powder formulation of active and inactive ingredients for direct compression. A cohesive ibuprofen powder was coprocessed with a coating material, a binder (polyvinylpyrrolidone K25), and a superdisintegrant (crospovidone). Magnesium stearate (MgSt), L-leucine, and silica were selected as coating materials (1% w/w). A coprocessed powder without any coating material was employed as a control. Coating with MgSt, L-leucine, or silica produced significantly improved powder flow in comparison to the control batch. Robust tablets were produced from the processed powders for each coating material. The tablets compacted using the coated powders with MgSt or L-leucine also exhibited significantly lower tablet ejection forces than the control batch, demonstrating their lubrication effect. Furthermore, the disintegration time and dissolution rates of these tablets made of the formulations coprocessed with lubricants were enhanced, even for those coated with the hydrophobic material such as MgSt that has been previously reported to inhibit dissolution. However, the tablets made with silica-coated powders would not disintegrate. This study indicated the feasibility of a single-step dry coating process to produce powders with both flow-aid and lubrication effects, which are suitable for direct compression.

Introduction

Oral solid dosage forms (primarily tablets) are the most commonly used drug delivery systems. Tablets offer convenient drug administration,[1] are generally more stable than comparable liquid forms, and are cost-effective.[2] During the formulation and manufacturing of oral solid dosage forms, tableting problems may arise from the properties of particles, including small particle size distributions, particle shape factors, and a range of particle surface properties, which may cause flowability or tabletability issues.[3,4] In the pharmaceutical industry, dry or wet granulation has been traditionally applied as the most popular forms of such transformation and modification to overcome the flowability problems caused by cohesive powders.[5] However, these traditional granulation approaches generally require complex processing steps, high cost of infrastructure, and increased risk of product failure and contamination.[6]

In this context, direct compression (or compaction) approaches are attractive as the continually modernizing pharmaceutical industry strives to improve its manufacturing output while reducing operational cost and process risks.[7] In contrast to wet or dry granulation, direct compression offers the potential advantages of a simple and lower-cost manufacturing process, with reduced risk of contamination and heat- and solvent-induced instability.[8,9] Direct compression requires that the powder blend of excipients and active pharmaceutical ingredients has suitable flow, uniformity, compactibility, and lubrication.[7,10] To meet these requirements, relatively large particles or large amounts of excipients must be used.[9] Many active pharmaceutical ingredient powders have poor flowability resulting in problems with blending,[11,12] albeit the combined flowability and uniformity properties of the powder blend are key features for direct compression.[6,7]

High-shear mechanical dry particle coating has been reported as a simple and efficient technique to improve flowability of cohesive

* *Correspondence to:* Qi (Tony) Zhou (Telephone: +1 7654960707; Fax: +1 7654946545) and David A.V. Morton (Telephone: +61 399039523; Fax: +61 399039583).
E-mail addresses: tonyzhou@purdue.edu (Q.T. Zhou), david.morton@monash.edu (D.A.V. Morton).

http://dx.doi.org/10.1016/j.xphs.2016.07.017
0022-3549/

Table 1
Formulations of Tablets (20-g/Batch, 100 mg/Tablet)

Batch	Amount in the Formulation (w/w)			
	Ibuprofen	Coating Material (MgSt, L-Leucine, or Silica-R972)	PVP K25	Kollidon CL-F
Control batch	85%	0	10%	5%
With coating material	84%	1%	10%	5%

powders.[13] In general, dry coating is simpler, cheaper, quicker, and more environmentally acceptable than the solvent-based coating alternatives because no solvent is used.[14,15] There are several types of dry coating devices and systems available including those termed as mechanofusion,[16] hybridizer,[17] comil,[18,19] fluid energy mills,[20] magnetically assisted impaction coater,[20,21] and laboratory resonant acoustic mixer.[15] The principles they share in common are the employment of high-energy and high-shear processes to coat additive "guest" excipients onto the surfaces of "host" particles.[22] Dry coating has been found to be an effective and efficient approach for dry particle coating,[23,24] which showed promising potential to facilitate direct compression by improving flowability of cohesive powders.[18,25,26] Previous studies have also illustrated the potential scale-up capability of mechanofusion process: flowability data of mechanofused lactose powder (1% w/w MgSt coating) are comparable between those produced by a lab-scale machine (Nobilta-AMS Mini; powder load up to 0.1 L; cohesion, 0.36 kPa; flow function, 11.7)[27] and by a pilot-scale one (Nobilta-130, powder load up to 0.5 L, Hosokawa Micron Corporation; cohesion, 0.47 kPa; flow function, 10.7),[16] albeit the scale-up capability of mechanofusion to the manufacturing scale has not been tested. To date, most studies focus on coating of drug or excipient cohesive powders, and few studies have addressed the feasibility to use dry coating as a single-step process to prepare powder mixture formulations containing both drug and excipients that are suitable for direct compression.

Therefore, the primary aim of this study was to test the feasibility of direct compression of dry coated powder mixtures that were produced by a single mechanofusion step. In this study, a fine cohesive ibuprofen powder was selected as a model high-dose drug with a low melting point and poor solubility in water. Cohesive ibuprofen powders were coprocessed with varying coating materials, a binder, and a disintegrant. Powder flowability, tabletability of such processed powders, and dissolution behavior of the corresponding tablets were examined.

Materials and Methods

Materials

Ibuprofen powder (Lot IB1T1570), polyvinylpyrrolidone (PVP K25), and Kollidon® CL-F (crospovidone, Lot 14682609T0) were donated by BASF (Ludwigshafen, Germany). Magnesium stearate NF (MgSt, Lot 1203000003) was provided by Mallinckrodt Chemicals (Phillipsburg, NJ). Hydrophobic fumed silica Aerosil® R972 (silica, Lot 3152040121) was donated by Evonik (Evonik Industries AG, Hanau, Germany). L-Leucine (Lot 110M0049V), potassium phosphate monobasic, sodium dodecyl sulfate, and sodium hydroxide were all purchased from Sigma-Aldrich (St. Louis, MO).

Methods

Preparation of Dry Coated Powders

The composition of the tablets is provided in Table 1. Approximately 20-g batches of active and inactive ingredients were weighed and manually preblended using a spatula in a 125-mL glass vessel and then transferred to the mechanofusion processing chamber. The powder mixtures were processed using an AMS-Mini Mechanofusion system (Hosokawa Micron Corporation, Osaka, Japan) with a Nobilta processing configuration. The mechanofusion process was conducted by a slow increase in speed up to 900 rpm over 1 min and remaining this speed for a further 5 min.[25] Cooling water (22°C ± 2°C) was applied *via* circulation through an incorporated jacket. Processed sample powders and their corresponding tablets were denoted by relevant guest material as MgSt, L-leucine, and silica. As a comparison, the powder mixture mechanofused with ibuprofen, binder, and superdisintegrant but without any coating guest material was denoted as a control batch.

Powder Densities and Carr Index

Poured density (ρ_p) and tapped density (ρ_t) were measured *via* previously reported methods with tapping requiring 1250 taps in an automatic tapper (AUTOTAP™, Quantachrome Instruments, Boynton Beach, FL) set with a 3.18-mm vertical travel at a tapping speed of 260 tap/min. Each measurement was run in triplicate. Carr Index (CI)[28] was calculated according to the obtained values of poured density and tapped density.

Particle Sizing

Particle size distributions of raw materials and the formulations were measured by laser diffraction (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using a dry dispersing unit. A small amount of sample powder (0.3-0.5 g) was dispersed at 1 bar using the dry dispersion feeder system and analyzed by a parallel laser beam diffraction unit. Dispersion pressure (1 bar) was chosen based on pressure titration tests at different dispersion pressures ranging from 0.5 to 3.0 bar. Three replicates of each sample were measured, and the volumetric particle size (D_{10} [diameter at 10% undersize], D_{50} [diameter at 50% undersize], and D_{90} [diameter at 90% undersize]) was calculated using the Sympatec Windox 5.0 software.

Particle size distributions of the formulations were also measured using a Morphologi G3 (Malvern Instruments, Worcestershire, UK). The Morphologi G3 is an optical microscope image analysis–based system, which permits not just particle size distributions to be directly measured, but also the morphological characteristics of statistically valid high numbers of particles. Particle recognition software provides number- and volume-based statistics. Each sample was dry dispersed onto a glass plate at a standardized injection pressure of 1 bar using an integral sample dispersion unit. The measurement for each sample was performed with 3 replicates. The particle size distribution (circle equivalent diameter) shown was calculated as D_{10} (diameter at 10% undersize), D_{50} (diameter at 50% undersize), and D_{90} (diameter at 90% undersize) by the inbuilt software and the results were averaged.

Powder Flow and Fluidization Properties

Powder flow and fluidization properties were measured using a Freeman FT4 system in the shear cell and aeration modules, respectively (Freeman Technology, Worcestershire, UK). A detailed description of the instrument has been addressed previously.[29,30] Briefly, in the shear cell test, a pre-shear normal stress of 9 kPa