A Prediction Model for Monitoring Ribbed Roller Compacted Ribbons

PHAM V. QUYET, ASIM K. SAMANTA, CELINE V. LIEW, LAI W. CHAN, PAUL W. S. HENG

GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543

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ABSTRACT: The application of near infrared (NIR) spectroscopy for real-time monitoring of the critical quality attributes of ribbed roller compacted ribbons was studied. Three NIR probes (QR 200, QR 400, and QR 600) of lens diameters, 200, 400, and 600 μm, respectively were used at various fixed distances from the ribbon surface to determine the calibration model with optimum predictive ability for monitoring the roller compaction process. The ribbon attributes studied were micronized chlorpheniramine maleate concentration, roll force, roll speed, ribbon density, and tensile strength. The custom-made belt conveying system was used to simulate the ribbon manufacturing process for NIR spectra capture. Simulation results obtained were then compared with the experimental results. The outcome of this study indicated that QR 400 was the best NIR probe for modeling, followed by QR 200 and QR 600. Of the five spectra measuring distance settings (d = 0.3, 0.6, 0.9, 1.2, and 1.5 mm), there was good correlation between simulation and experimental findings indicating that the calibration models for bigger probe sizes were better if the measuring distance was smaller. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2667–2678, 2013

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INTRODUCTION

Roller compaction is a popular dry granulation process used by the pharmaceutical industry. Its operation involves two counter rotating rolls which draw and consolidate the powder feed into flake-like compacts. As this granulation process does not involve any solvent, no heat associated drying will be needed. Hence, it is particularly suitable for heat and moisture sensitive materials.[1,2]

Granulation by roller compaction is attractive for large-scale manufacturing because it requires fewer unit operations, smaller equipment footprint, shorter manufacturing process time, and hence, lower production costs.[3] However, the fundamental mechanism of compaction is complex because of inconsistencies in material and process attributes.[4–6] The variability of raw material properties, such as particle size and particle morphology, as well as process variables, such as feed screw speed (FSS), roll speed (RS), roll gap, and roll surface, have been shown to significantly affect the ribbon attributes which eventually could impact granule size distribution, compressibility, content uniformity, and flow characteristics after milling.[3,7–9]

The US Food and Drug Administration (FDA) encourages the use of process analytical technology (PAT) tools for timely measurements of critical attributes during manufacture.[25] In-line monitoring of the roller compaction process has been studied extensively and numerous successful applications of near infrared (NIR) have been reported in the literature.[10–15] Many of these studies were based on rolls that had smooth surfaces. However, axially corrugated roll surface is preferred because it gives better gripping capability, thereby increasing the bulk density (BD) of less dense materials[6] and allowing for a faster and more-consistent production process.

Although the ribbed ribbon has these advantages in actual manufacturing, the experimental surface of the ribbed ribbons are expected to pose considerable difficulties when building up the calibration models for real-time process monitoring. Both static and dynamic spectra capturing modes had been studied.

Correspondence to: Paul W. S. Heng (Telephone: +65-6516-2930; Fax: +65-6779-1554; E-mail: phapaulh@nus.edu.sg)

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Preliminary results showed that dynamic mode gave models with much better prediction ability for this type of ribbon, hence, this work focused on the dynamic spectra capturing mode using a custom-built conveying system to transverse the ribbon across the NIR probe lens during spectra acquisition. Although the ribbon was in motion, the actual distance between the NIR probe and the ribbed ribbon surface would be changing continuously because of the undulations of the surface of the ribbed ribbon. This would add another layer of complexity, uncertainty, and inaccuracies for process modeling. Therefore, it was of critical importance not only to build the calibration model but also to compare it with a rigorously derived mathematical derivation to have a deeper understanding of the ribbed ribbon compaction process and to identify any potential mismatch. From the analysis of mismatched patterns, conclusions could be achieved with better accuracy and the best experimental parameters were identified with greater confidence.

Thus, this study aimed at building a calibration model for a simulated ribbon compaction process using partial least square (PLS) analysis and to compare the findings with a mathematical model. The role of the mathematical model was important because it provided unbiased adjustments for the spectra-acquired results.

MATERIALS AND METHODS

Materials

The ribbon formulation consisted of chlorpheniramine maleate (CPM, BP grade, China), magnesium stearate (MgSt, Sigma–Aldrich, Germany), microcrystalline cellulose (MCC, Avicel PH102, FMC Biopolymer, Philadelphia, Pennsylvania) and lactose (SpheroLac 100, Meggle AG, Wasserburg, Germany).

CPM was jet milled using AFG100 system (Hosokawa, Augsburg, Germany) at a classifying speed of 7500 rpm and pressure of 0.4 MPa to produce micronized CPM (μCPM) of mean particle size of 10 μm. Ambient conditions for all experiments were at 25 ± 2°C and 50 ± 5% relative humidity (RH).

Experimental Methods

Ribbon Feed Preparation

A weighed amount of μCPM was first premixed with lactose in a 10 L high shear mixer (UltimaPro, Collette NV, Wommelgem, Belgium) at an impeller speed of 200 rpm for 3 min. Next, the powder blend was transferred into a 15 L intermediate bulk container (IBC) bin blender (SP15, GEA Pharma Systems, Eastleigh, UK) with the prism attached and blended with MCC at a rotational speed of 10 rpm for 10 min. MgSt was added and powder blend was mixed for a further 5 min. MgSt in the powder blend lowers the sticking of compacted powders to the axially corrugated roll surfaces.[14,16–18]

Table 1. Codes for Batches of Ribbons Prepared by Roller Compaction under Different Conditions

	Roll Force (kN)				
	40	50	60	70	80
μCPM (%)	Batch code				
0	EXP 1	EXP 2	EXP 3	EXP 4	EXP 5
2	EXP 6	EXP 7	EXP 8	EXP 9	EXP 10
4	EXP 11	EXP 12	EXP 13	EXP 14	EXP 15
6	EXP 16	EXP 17	EXP 18	EXP 19	EXP 20
8	EXP 21	EXP 22	EXP 23	EXP 24	EXP 25

Roller Compaction

Two factors, μCPM concentration in powder blend and roll force (RF), at five different levels were studied. A full factorial design was used to generate five^2 or 25 experiments. The five different powder blends were prepared and compacted (Hosokawa® Bepex Pharmapaktor L200/30P, Osaka, Japan) at five different RFs (40, 50, 60, 70, and 80 kN), as shown in Table 1. The rolls were of 20 cm diameter and each with 3 cm width axially corrugated roll surfaces. The roller compactor was operated in automatic mode with a RS of 2.6 rpm. This RS was maintained by automatic adjustment of the vertical feeding screw via a feedback control mechanism. For each run, the compaction process was allowed to operate for 1 min to reach steady state before the ribbon product was collected. Each ribbon batch collected was placed on a 2 mm aperture mesh sieve and shaken at 70 shakes per min for 2 min on a sieve shaker (KS 1000, Retsch, Haan, Germany) to remove uncompacted powder adhering on the ribbon surface. The ribbons were collected and stored at 25 ± 2°C and 50 ± 5% RH for at least 3 days before measurement.

μCPM Content Determination of Flakes

A laboratory validated ultraviolet (UV) spectroscopic method was used to determine μCPM content in each batch of NIR scanned flakes. Approximately 1 × 1 cm mid-area from five randomly selected flakes from each batch was cut and crushed into powder. From the crushed powder, 500 mg of accurately weighted power sample was transferred to 200 mL volumetric flask and volume adjusted with distilled water. Sonication of the sample solution was carried out for complete disintegration and dissolution of μCPM. From the volumetric flask, 20 mL aliquot was withdrawn, centrifuged at centripetal acceleration of 1015 g for 5 min, and the resultant supernatant solution was analyzed for CPM content by UV absorption [UV-3101