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Influence of relative humidity during coating on polymer deposition and film formation

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ABSTRACT

The influence of relative humidity in the pan during coating on polymer deposition and film formation was investigated. Four tablet substrates, differing in hydrophobicity, porosity, and surface roughness, were prepared and coated with Eudragit® RS/RL 30 D (8:2 ratio). The spray rate and atomization air pressure were varied to create two distinct micro-environmental conditions in the coating pan. PyroButton data logging devices placed directly in the pan were found to more accurately reflect the relative humidity to which tablets were exposed in comparison to measurements taken at the exhaust. Polymer deposition was shown to be influenced by the properties of the substrate, rather than the processing conditions used during coating, with higher polymer weight gains observed for the more porous tablets. Differences in the film-tablet interface and in the release performance of the coated products, however, were attributed to both the relative humidity in the pan and tablet porosity. Overall, this study demonstrated that a more humid coating process (86% vs 67%) promoted surface dissolution and physical mixing of the tablet ingredients with the forming film and the extent of this phenomenon was dependent on the tablet porosity.

1. Introduction

After the launch of the Quality by Design approach in the pharmaceutical industry in 2004 (FDA, 2004), the use of Process Analytical Technologies and statistical Design of Experiments (DoE) has rapidly increased. Such tools, aimed at improving fundamental knowledge of pharmaceutical processes, require a scientific approach to study the effects of process variables on product performance.

For the application of polymeric films to solid substrates, the impact of a single or a few variables at a time on the process or performance of coated dosage forms has traditionally been studied. For example, Brock et al. (2014) performed a DoE at pilot scale with drum load, drum speed, spray rate, run duration and spray pressure as variables, to identify critical process parameters for inter-tablet coating uniformity. In another study, Khan et al. (2001) focused on variables related to the formulation of the coating suspension and their impact on spreading coefficients of hydroxypropyl methylcellulose solutions.

Polymeric film coating, however, is a highly complex process. Indeed, substrate characteristics, coating formulation, equipment and processing conditions can affect polymer deposition and film performance (Wilson and Crossman, 1997; Freireich et al., 2011; Cunningham et al., 2001; Wesseling et al., 1999; Mehta, 2008). In addition, these variables may be strongly inter-connected (Pandey et al., 2014a). Another limitation to a more complete understanding of how variables impact coating performance is that process controls typically rely on measurements taken in locations outside the substrate bed (*i.e.* in the exhaust plenum). Furthermore, mathematical models which have been developed do not account for heat losses during processing and, hence, tend to deviate from experimental results, in particular when used for scaling-up (Zacour et al., 2014). For a more thorough understanding of coating processes, studies should correlate product performance to the actual coating conditions to which the substrates are exposed.

PyroButton data loggers are tablet-sized devices that can be placed directly in the substrate bed to monitor the temperature (T) and relative humidity (RH) conditions to which the substrates are exposed during the coating process, the so-called micro-environmental conditions. PyroButtons have been used to investigate the impact of micro-environmental conditions on the delamination of bi-layer tablets (Zacour et al., 2014), the tendencies towards logo-bridging (Pandey et al., 2014b), swelling of the surface of injection

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molded hydroxypropyl cellulose capsules (Macchi et al., 2016) and stability of moisture sensitive drug products (Kestur et al., 2014). Data recorded by the PyroButtons correlated well to the characteristics of coated products, whereas correlation between these characteristics and traditional measurements (*e.g.* exhaust air temperature) was poor. In some of these previously published studies, process scaling was also investigated and limitations in the traditional scale up rules were highlighted.

To date, no studies have focused on the impact of micro-environmental conditions on polymer deposition and film formation. Hence, the objective of the current study was to determine the influence of the RH inside the coating pan on polymer deposition and film formation. Tablets with different hydrophilicity, porosity and surface roughness were coated with a suspension of Eudragit® RS and RL under two distinct processing conditions created by adjusting the spray rate (SR) and the atomization air pressure (AAP). PyroButtons were used to record T and RH during coating and these data were correlated to the characteristics and performance of the coated tablets.

2. Material and methods

2.1. Materials

The following materials were used: acetaminophen fine powder (APAP) was purchased from Alfa Aesar (UK); microcrystalline cellulose, Avicel® pH 102, was kindly donated by FMC Co. (PA, USA); fumed silica, CAB-O-SIL® M-5P, was donated by Cabot Co. (IL, USA); magnesium stearate (MgSt) and talc were purchased from Spectrum Chemical Mfg Corp. (CA, USA); Eudragit® RL 30 D and Eudragit® RS 30 D were donated by Evonik (Germany); triethyl citrate (TEC) was donated by Vertellus Specialties Inc. (IN, USA); rhodamine B and trifluoroacetic acid were purchased from Sigma-Aldrich (MO, USA); LC–MS grade methanol, OmniSolv®, was purchased from EMD Millipore (MA, USA); HPLC grade water was produced by a Cascada™ LS-water Purification System (Pall Corporation, NY, US).

2.2. Methods

2.2.1. Tablets substrates

Tablets formulations (A and B) are reported in Table 1. The amount of MgSt was varied to produce tablets with different hydrophilicity. While not typical for commercial tablet production, the high level of MgSt (4%) was specifically selected in this study to create a more hydrophobic surface rather than for its lubricant functionality (Rowe, 1977). Acetaminophen, Avicel pH 302 and fumed silica were blended in a V-shell blender for 15 min, followed by the addition of MgSt and blending for another 5 min.

Powders were compressed to 5 or 10 Kp using a Stokes 511-7 single punch compacting press to prepare tablets with different surface roughness and porosity (A5, A10, B5 and B10). Both convex and flat faced tablets were prepared. Because of their shape, the convex tablets would assure minimum sticking during the coating process (Macchi and Felton, 2016) and thus these tablets were used for both coating and dissolution testing. In contrast, the flat faced tablets were produced primarily for the initial characterization experiments (*i.e.* contact angle testing/surface wettability, surface roughness and porosity).

Table 1
Tablets formulation (% w/w).

	A	B
Acetaminophen	16.7	16.7
Avicel pH 302	82.6	79.1
Fumed silica	0.2	0.2
Magnesium stearate	0.5	4.0

2.2.2. Preparation of the coating suspension

Commercially available Eudragit® RS 30 D and RL 30 D in a 8:2 ratio were plasticized with TEC (20% w/w, based on the dry polymer weight) and stirred for at least 30 min. Separately, talc (50% w/w based on the dry polymer weight) was dispersed in water (sufficient to decrease the solid contents of the final suspension to 20%) by means of a homogenizer. After pouring the talc suspension into the Eudragit mixture, the fluorescent marker rhodamine B (0.001% w/w, based on the dry polymer weight) was added and the resulting formulation was filtered through a 0.3 mm sieve and maintained under stirring during the coating process.

2.2.3. Coating process and curing

Two batches of 800 tablets each were coated until a theoretical 6% weight gain of polymer was applied. Each batch consisted of 200 convex tablets for each type of substrate. The different types of cores were marked using colored markers before coating for identification. A LDCS-3 Hi-coater (Vector Corporation, IA, USA) equipped with a 1.3 L perforated pan was used. Process parameters for coatings C1 and C2 are reported in Table 2. Tablets were then cured at 40 °C for 2 h and stored at ambient conditions for 7 days before further testing. Curing of aqueous-based polymeric dispersions is routinely required to promote coalescence of the film (Felton, 2013).

2.2.4. Monitoring of temperature and relative humidity

T and RH measurements during coating were recorded every 10 s by PyroButton® data-loggers (PyroButton-TM, Opulus Ltd., Philadelphia, PA). Data loggers calibration and programming, as well as their location in the coating equipment have previously been described (Macchi et al., 2016); briefly, two PyroButtons were placed directly in the pan with the tablets during the pre-heating stage and allowed to tumble freely with the substrates. A third PyroButton was attached in the exhaust air duct by means of double-sided tape, close to the probe where the exhaust temperature (T_{exh}) is read. T and RH conditions were monitored starting from the pre-heating step (5 min prior to initiation of spraying) to the end of each run. After each run was completed, the PyroButtons were removed and cleaned with methanol. Next, T and RH measurements were downloaded from the data loggers. Mean T and RH values registered by each of the three data loggers during the two coating runs were calculated at the steady state condition (5–20 min). Subsequently, also the T and RH values registered by the PyroButtons placed in the tablet bed were averaged, in order to have a single value for bed T and RH for each coating process. T_{exh} during each coating run was recorded manually at 5 min intervals and mean values were then calculated.

2.2.5. Characterization of tablets

2.2.5.1. Profilometry. The roughness of the surface of flat faced uncoated tablets was determined using a Dektak 150 Surface Profiler (Veeco, NY, USA). The tip radius was 12.5 μm, the scanned length was 1500 μm; the scan resolution was 0.069 Å and measurement range and duration were 65.5 μm and 120 s, respectively.

The arithmetic average roughness (Ra) parameter was calculated for each tablet type using Eq. (1), while Eq. (2) was used to calculate the geometric average roughness (Rq):

$$Ra = \frac{\sum_{n=1}^{N} |Z_n - Z^-|}{N} \quad (1)$$