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Research Paper

Influence of temperature and relative humidity conditions on the pan coating of hydroxypropyl cellulose molded capsules

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ABSTRACT

In a previous study, hydroxypropyl cellulose (HPC)-based capsular shells prepared by injection molding and intended for pulsatile release were successfully coated with 10 mg/cm^2 Eudragit® L film. The suitability of HPC capsules for the development of a colon delivery platform based on a time dependent approach was demonstrated. In the present work, data logging devices (PyroButton®) were used to monitor the microenvironmental conditions, *i.e.* temperature (*T*) and relative humidity (RH), during coating processes performed under different spray rates (1.2, 2.5 and 5.5 g/min). As HPC-based capsules present special features, a preliminary study was conducted on commercially available gelatin capsules for comparison purposes. By means of PyroButton data-loggers it was possible to acquire information about the impact of the effective *T* and RH conditions experienced by HPC substrates during the process on the technological properties and release performance of the coated systems. The use of increasing spray rates seemed to promote a tendency of the HPC shells to slightly swell at the beginning of the spraying process; moreover, capsules coated under spray rates of 1.2 and 2.5 g/min showed the desired release performance, *i.e.* ability to withstand the acidic media followed by the pulsatile release expected for uncoated capsules. Preliminary stability studies seemed to show that coating conditions might also influence the release performance of the system upon storage.

1. Introduction

Film coating of solid dosage forms is frequently used in the pharmaceutical industry to fulfill several needs, either esthetic, stability-related or functional, *e.g.* modified-release dosage forms [1]. Pan coaters and fluid-bed systems are the most widely used apparatus to apply polymer coatings. Irrespective of the equipment employed, film coating involves the atomization of polymer solutions or dispersions followed by impingement of the atomized droplets onto the substrate surface and subsequent solvent evaporation to form the film.

When aqueous polymeric suspensions are employed, coalescence of the discrete polymer spheres needs to take place. In general, when dealing with aqueous dispersions the formation of a continuous film and its adherence to the substrates strongly depend on the rate of solvent evaporation, which is driven by the thermodynamic conditions in the coating pan, mainly temperature (*T*) and relative humidity (RH). Adjustments in processing parameters to achieve the same coating conditions are necessary also in case of transfer to coating pans of different shapes and during scale-up [2].

Because *T* and RH play such a key role in film formation, the monitoring of the actual microenvironment experienced by substrates during their coating assumes essential importance. The exhaust air temperature has been typically considered the monitoring parameter most representative of the conditions of cores in the pan [3]. However, such macroscopic measurement captured by sensors often placed far from the pan itself does not fully char-

Abbreviations: HPC, hydroxypropyl cellulose; T, temperature; RH, relative humidity; SR, spray rate; P_f, PyroButton data-logger fixed in the exhaust air plenum; P_b, PyroButton data-logger placed in the tablets bed; T_{exh}, exhaust temperature read by the probe of the coating equipment; $t_{10\%}$, time to 10% drug release; $t_{90-10\%}$, time elapsed between 10% and 90% drug release.

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acterize the actual conditions experienced by cores [4]. This limitation can be partially overcome by the use of infrared guns to measure the *T* of the surface of the substrate bed during the process. However, the need for opening the pan door during the coating run, although for a short time, results in perturbations of the environmental conditions inside the coating pan. Moreover, no information about the RH can be obtained with either the probes coating equipment is equipped with or infrared guns. Hence, traditional measurements cannot fully assess the coating process or the relationship between the *T* and RH in the pan and the coating performance. Such limitation becomes a major issue when coating substrates for which *T* and, in particular, RH have a strong impact on the outcome of the process, *e.g.* gelatin capsules [5]. Only very recently, PyroButton®, a tablet-size temperature/humidity datalogger, has been proposed to record the microenvironmental conditions in the pan coater during film application on solid tablet cores [6–10]. PyroButton data-loggers can be fixed in one location or allowed to move freely with the cores in the coating pan.

In the present work, PyroButton data-loggers were used to monitor conditions in the pan during the enteric coating of novel Chronocap™ capsules, in order to correlate *T* and RH with the physical characteristics and release performance of coated systems. Chronocap™ is a capsule-shaped shell made of hydroxypropyl cellulose (HPC) prepared by injection molding and intended for delayed/pulsatile release of a variety of fill formulations, *e.g.* powders, granules, pellets, and solid dispersions [11,12]. Prototypes filled with different preparations were shown to provide, both *in-vitro* and *in-vivo*, the liberation of the contained drug after a lag time, which was dependent on the shell composition and thickness [12,13]. One of the possible applications of delayed/pulsatile release dosage forms is colon targeting. Such a time-dependent approach to achieve colonic delivery relies on the relatively constant small intestinal transit time (SITT; 3 h ± 1 standard error) of dosage forms [14–16]. The duration of residence in the stomach, however, is unpredictable and this variability can be overcome by the application of a gastroresistant film that dissolves in the small intestine upon the significant increase in the luminar pH. Accordingly, the Chronocap™ shell was considered as a substrate for the development of a time-based colonic delivery system [17]. Preliminary work showed feasibility for the Chronocap™ system to be coated with an aqueous suspension based on the Eudragit® L enteric polymer and the achievement of the desired release performance. However, samples withdrawn from the coating pan at different time points during the process showed a slight increase in the shell wall thickness, probably due to the swelling of the HPC upon contact with the sprayed aqueous polymeric formulation. In the present work, the ability of PyroButton devices to monitor the *T* and RH conditions experienced by the capsular cores during coating processes was exploited to evaluate the impact of process conditions on the physico-technological characteristics and release performance of the coated systems. Commercially available gelatin capsules were considered for comparison purposes.

2. Materials and methods

2.1. Materials

The following materials were used: hydroxypropyl cellulose (HPC), Klucel® LF (Eigenmann & Veronelli, Italy); polyethylene glycol (PEG) 1500 (Clariant Masterbatches, Italy); acetaminophen granules (APAP), Compap™ Coarse L (Mallinckrodt, MO, USA); Eudragit® L 30 D 55 (Evonik, Germany); triethyl citrate (TEC) (Vertellus Specialties Inc., IN, USA); trifluoroacetic acid (Sigma–Aldrich, MO, USA); LC–MS grade methanol, OmniSolv® (EMD Millipore, MA, USA); HPLC grade water; and size 2 hard-gelatin capsules (Capsugel, SC, USA).

2.2. Methods

2.2.1. Preparation of HPC capsule shells

A bench-top micromolding machine (BabyPlast 6/10P; Cronoplast S.L., Spain; Rambaldi S.r.l., Italy) was loaded with a mixture of Klucel® LF and PEG 1500 (90% and 10% w/w, respectively), prepared in Turbula® (Type T2C; WAB, Switzerland). Before use, HPC was dried in a ventilated oven for 24 h at 40 °C. Molded items of 600 μm nominal thickness were prepared by a mold with two interchangeable inserts for the manufacturing of matching caps and bodies, as previously reported (Zema et al. [12]). The technological characteristics and release performance of these capsule shells were evaluated after 7 days of storage at ambient conditions (24 ± 2 °C/55 ± 5% RH).

2.2.2. Coating of capsule cores

2.2.2.1. Filling of capsule shells. Gelatin capsules (Capsugel, SC, USA) and HPC-based capsules were manually filled with 150 mg of APAP granules. Unlike gelatin capsules, HPC capsules did not require sealing of the closing area prior to coating [17] because of their special locking mechanism [12]; hence, only gelatin capsules were manually band sealed, using a 20% w/v gelatin aqueous solution [18].

2.2.2.2. Preparation of the coating suspension. Commercially available Eudragit® L 30 D 55 dispersion was diluted to decrease the solid contents to 20% and plasticized with 20% w/w TEC (based on the dry polymer weight). After 30 min stirring, the suspension was filtered through a 0.3 mm sieve and maintained under stirring during the coating process. The amount of suspension required for each run in order to apply 10 mg/cm^2 of polymer on cores was calculated based on the total surface area of each type of capsule.

2.2.2.3. Coating process and curing. Batches of 500 capsules were coated in a LDCS-3 Hi-coater (Vector Corporation, IA, USA) equipped with a 1.3 L perforated pan. Coating conditions for gelatin and HPC capsules were as follows: bed air temperature, 30 °C; air pressure, 12 psi (82,737 Pa); and pan speed, 15 rpm. The spray rate (SR) was set at 1.2, 2.5 or 5.5 g/min. Samples sprayed for 1 min and at increasing coating levels were withdrawn during each run and replaced with marked placebos of the same capsule type to maintain batch size. Coated capsules were cured in a ventilated oven at 40 °C for 2 h. Testing was performed after 7 days of storage at ambient conditions (24 ± 2 °C/55 ± 5% RH).

2.2.2.4. Temperature and relative humidity monitoring. PyroButton data-loggers (PyroButton-TM, Opulus Ltd., Philadelphia, PA) were used to record *T* and RH (21-CFR-11 compliant, 17 × 6 mm diameter) (Fig. 1a and b). PyroButton devices were calibrated before use as described by Pandey et al. [8] and programmed to record data every 10 s. *T* and RH working ranges were 2–84 °C and 3–99%, and resolution was 0.5 °C and 0.64%, respectively.

One PyroButton® (P_f) was fixed in the exhaust air plenum by means of double-sided tape, close to the probe where the exhaust temperature (T_{exh}) is read. Two other data loggers (P_{b1}, P_{b2}) were placed in the pan with the capsules during the pre-heating stage and allowed to tumble freely with the capsule cores (Fig. 1c).

After a 5 min preheating (from −5 to 0 min), capsules were coated with 10 mg/cm^2 of polymer. Samples were withdrawn after 1 min from the start of the spraying and when theoretical 4, 8, and 10 mg of enteric polymer/cm^2 were applied. *T* and RH conditions during each coating run were monitored starting from the preheating step to the end of the runs. Since all the operator's actions were

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