Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 464–475
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Influence of processing parameters and formulation factors on the drug release from tablets powder-coated with Eudragit® L 100-55

Dorothea Sauer [a,*], Weijia Zheng [b], Lonique B. Coots [a], James W. McGinity [a]

[a] *Drug Dynamics Institute, The University of Texas at Austin, Austin, USA*
[b] *Novartis Institutes for BioMedical Research, Inc., Chemical and Pharmaceutical Profiling, Cambridge, USA*

Received 16 November 2006; accepted in revised form 27 February 2007
Available online 7 March 2007

Abstract

The aim of this study was to develop a dry powder coating process for chlorpheniramine maleate (CPM) tablets using Eudragit® L 100-55 as the delayed release polymer. Powder coating, a water and organic solvent-free process, was investigated as a method to prevent the migration of an ionizable, highly water soluble model drug into the polymeric film during the coating process. Eudragit® L 100-55 was pre-plasticized with triethyl citrate (TEC) using hot-melt extrusion at levels of 20%, 30%, and 40%, based on the polymer weight. The extrudate was subsequently cut into pellets and cryogenically ground into a fine powder. Talc was incorporated into the coating powder as an anti-tack agent. PEG 3350 was used as a primer for the powder coating of tablets with pre-plasticized Eudragit® L 100-55. The addition of polyethylene glycol 3350 (PEG 3350) to the pre-plasticized Eudragit® L 100-55 was necessary to enhance the adhesion of the coating powder to the tablet cores. PEG 3350 also improved film formation and coalescence of the polymeric particles due to its plasticization effects on the acrylic polymer. For comparison, theophylline tablets were also coated with pre-plasticized Eudragit® L 100-55. Theophylline was selected as a less water soluble model drug. The powder coating process was performed in a modified laboratory scale spheronizer. The drug release rate was dependent both on TEC content and the coating level. The stability of the powder-coated CPM tablets was confirmed at 25 °C/60% RH over a storage time of 12 weeks.

Keywords: Powder coating; Eudragit® L 100-55; Chlorpheniramine maleate; Theophylline; Enteric polymers; Film formation

1. Introduction

Although widely employed in other industrial applications since the 1950s, dry powder coating was not described in the pharmaceutical literature until the late 1990s. The primary advantage of this process is that it circumvents many limitations of established organic and aqueous coating systems for pharmaceutical products. The traditional use of organic solvents in coating processes creates environmental, toxicological, and safety-related concerns. Problems of aqueous coating are primarily due to the limited applicability for water-sensitive active ingredients [1], the migration of drugs into the polymer coatings during processing [2], and the physical aging of the polymeric films that leads to changes in the drug release rate during product storage [3–5].

The first approach to powder-coat pharmaceutical dosage forms was reported by Obara and coworkers in 1999 [6]. The process involved the direct application of polymeric particles and the simultaneous spraying of a mixture of a plasticizer and acetylated monoglyceride onto drug containing cores. An aqueous hydroxypropyl methylcellulose (HPMC) solution was applied during the curing step to improve film formation [6]. Pearnchob et al. modified the technique using an aqueous HPMC solution in combination with a plasticizer, while still separately feeding the polymer powder onto the solid substrates during the coating process [7–9]. Investigations from these researchers

* Corresponding author. Drug Dynamics Institute, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA. Tel.: +1 512 232 4088; fax: +1 512 471 7474.
E-mail address: sauer@mail.utexas.edu (D. Sauer).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.02.021

encompassed cellulose derivatives, the acrylic polymer Eudragit® RS, and shellac [7–9]. Both methods [6–9] required a minimal amount of water, and it was demonstrated that dry-powder coating compared to aqueous coating procedures generally required higher coating levels, higher plasticizer concentrations, and higher processing temperatures. Nevertheless, the processing time in dry-powder coating operations was significantly shorter due to the high solid content of the coating mixture.

Recently the dry coating method developed by Obara was modified by Kablitz et al. by replacing the anti-tacking agent talc with colloidal silicon dioxide and eliminating the use of water in the curing step [10].

A novel water and solvent-free powder coating technique was developed by Cerea et al. and Zheng et al. in 2004 [11,12]. This dry coating technique did not utilize water or any other liquid during the entire coating process. The process was successfully applied for the acrylic polymers Eudragit® RS PO, Eudragit® RL PO, and Eudragit® E PO for the coating of tablets to modify the drug release rate. Dry powder coating was shown to prevent the aging of the polymeric film, a phenomenon which has been reported for aqueous coated dosage forms during storage. The powder coating process itself consists of three steps, namely, priming, powder layering, and curing. To facilitate the direct application of the acrylic polymers onto the solid substrates, the solid Eudragit® RS PO and Eudragit® RL PO powders were pre-plasticized using a hot-melt extrusion process. The extrudates were subsequently cryogenically ground into a micronized coating powder [12]. The pre-plasticization step was not needed for Eudragit® E PO due to the low glass transition temperature of this polymer [11].

Eudragit® L 100-55, an anionic copolymer, is based on methacrylic acid and ethyl acrylate in a 1:1 ratio and has not been studied in dry powder coating applications. Its glass transition temperature was reported to be within the range of 124–129 °C [13,14].

The objective of the present study was to investigate the properties of chlorpheniramine maleate (CPM) and theophylline tablets that were powder-coated with pre-plasticized Eudragit® L 100-55. CPM is a freely water soluble drug. It was reported that CPM pellets required higher coating levels of the enteric polymer than pellets containing theophylline, a less soluble drug, in order to pass the dissolution specification in acidic media due to the migration of the drug into the Eudragit® L 30 D-55 coating [2].

Powder coating, a water and organic solvent-free process, was employed as a method to prevent the migration of the highly water soluble drug CPM into the film coating. The drug release properties of the powder-coated tablets as well as storage stability under accelerated storage conditions were studied. Film formation and surface morphology of powder-coated tablets were characterized, and the function and influence of the primer on powder adhesion and film formation were studied.

2. Materials

Eudragit® L 100-55 was donated by Degussa Corp. (Piscataway, NJ). Chlorpheniramine maleate USP/NF, anhydrous theophylline USP, magnesium stearate NF, and lactose monohydrate NF were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate NF (TEC) was donated by Morflex Inc. (Greensboro, NC). Talc USP (Imperial 500) was supplied by Luzenac America, Inc. (Centennial, CO). Polyethylene glycol (PEG) 3350 NF was donated by The Dow Chemical Company (Midland, MI). Microcrystalline cellulose (MCC, Avicel® PH-101) was donated by FMC BioPolymer (Newark, DE). Polyvinylpyrrolidone K-30 (PVP, Kollidon® 30) was supplied by BASF Corp. (Mt. Olive, NJ). Colloidal silicon dioxide (CAB-O-SIL® M-5P) was donated by Cabot Corporation (Billerica, MA).

3. Methods

3.1. Coating powder preparation and characterization

The pre-plasticization process for Eudragit® L 100-55 was based on the method reported by Zheng et al. [12] for Eudragit® RS and Eudragit® RL PO. After combining Eudragit® L 100-55 with TEC (20%, 30%, or 40% based on the polymer weight) in a high shear mixer, the powder blend was extruded using a single screw extruder (Randcastle Model RC 0750, Cedar Grove, NJ). The extruder temperature zones were set to: zone 1 = 80 °C, zone 2 = 110 °C, zone 3 = 115 °C, and die = 120 °C. A cylindrical die with an inner diameter of 6 mm was used. The extrudate was subsequently cut into pellets with a Randcastle RCP-2.0 pelletizer and then cryogenically ground into a fine powder using a CF Mikro-Bantam Cryogenic Grinder (Micron Powder Systems, Summit, NJ). To obtain a more uniform particle size distribution and exclude fines and large particles, the ground pre-plasticized polymer was sieved by mechanical shaking for 15 min. The particle size fraction between 100 and 200 mesh (75–150 μm) was used for the dry powder coating experiments.

Laser light diffraction was employed to analyze the particle size distribution of the coating powder using a Malvern Mastersizer S (Malvern Instrument Limited, Malvern, Worcestershire, UK). D_v 10, D_v 50, and D_v 90, the cumulative percent undersize, were determined using the diffractive index of Eudragit® L 100-55 ($n_D^{20} = 1.3899$). The measurements were performed in triplicate in purified water ($n_D^{20} = 1.3300$).

The TEC content in the extrudates was determined at a wavelength of 210 nm using a Waters high performance liquid chromatography (HPLC) system (Waters, Milford, MA) equipped with a photodiode array detector (Model 996). Depending on the TEC concentration, 500 mg (20% and 30% TEC) or 300 mg (40% TEC) of processed polymer was initially dissolved in 50 mM, pH 7.4, buffer and then 1:2 diluted with 50 mM, pH 2.5, phosphate buffer to