International Journal of Pharmaceutics 516 (2017) 380–391

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A novel approach for dry powder coating of pellets with Ethylcellulose. Part I: Evaluation of film formulation and process set up

Beatrice Albertini*, Serena Bertoni, Cecilia Melegari, Luisa Stella Dolci, Nadia Passerini

Department of Pharmacy and BioTechnology, University of Bologna, Via S. Donato 19/2, 40127 Bologna, Italy

ARTICLE INFO

Article history:
Received 26 July 2016
Received in revised form 22 November 2016
Accepted 23 November 2016
Available online 25 November 2016

Keywords:
Ethylcellulose
Films
Plasticizers
Dry powder coating
Placebo pellets
High-shear granulator

ABSTRACT

An innovative dry powder coating technology was developed in a high-shear granulator using ethylcellulose (E10) as polymer. Several solid plasticizers were investigated with the aim of decreasing the polymer Tg at least to the highest possible working temperature (80 °C). DSC analysis of physical mixtures of E10 and plasticizers evidenced that lauric acid (LA) was the most effective plasticizer. In order to reach the target temperature a liquid plasticizer, oleic acid (OA), was introduced in the coating formulation. Free films were then prepared and the target minimum film forming temperature (MFFT) was established in the range 70–80 °C. Depending on the LA:OA weight ratio, Kollidon VA64 was included to decrease the LA recrystallization, while talc served as anti-sticking agent. Curing at the MFFT ensured the formation of homogeneous and stable films with good stability on storage. The dry powder coating process of placebo pellets was then developed, consisting of a combination of liquid assisted and thermal adhesion methods. The best coating formulations in terms of yields, coating efficiency (expressed as Relative Standard Deviation of the weight applied) and low pellets aggregation were based on E10:LA:OA in a weight ratio of 65:20:15 and 60:20:20. Moreover pellets remained stable after 1 year of storage (25 °C/60% R.H.).

1. Introduction

Conventional technologies used in pharmaceutical film coating processes involve the atomization of polymeric systems as solution or suspension in volatile organic solvents and/or aqueous vehicles. Nowadays, the use of aqueous systems remains the preferred manufacturing approach due to the absence of solvent toxicity, increased process safety and lower manufacturing costs (Cerea et al., 2004; Bose and Bogner, 2007; Sauer et al., 2013). Even in light of the benefits of aqueous systems, there are several cases where aqueous systems are inappropriate and organic solvent coatings may be necessary. For example, when the active ingredient is sensitive to water and when migration of water with aqueous systems may occur during the coating process or during storage, compromising the product quality (Sauer et al., 2013). Water-based coatings have also the disadvantage of requiring high energy to evaporate the medium and frequent problems of nozzle clogging. All these limitations prolong processing time.

Over the last decade, dry powder coating technology for pharmaceutical applications has gained increasing attention (Obara et al., 1999; Kablitz et al., 2006; Cerea et al., 2008; Kablitz and Urbanetz, 2009) and the first review of this process has been published three years ago (Sauer et al., 2013) in a special issue of IJP, entitled “Progress in film coating” (Siepmann et al., 2013). This process has been recognized to be an environmentally-friendly and a promising coating technology to overcome the above mentioned disadvantages associated with organic and aqueous coating systems. A range of dry powder coating technologies have been developed in both academic and industrial settings and they can be generally classified into three major types based on the layer formation process: thermal adhesion (melt coating), liquid assisted and electrostatic methods. These techniques may require either specific equipment, as in the case of electrostatic coating, or the use of novel excipients and specific formulations to provide acceptable manufacturability and product quality (Smikalla et al., 2015; Sauer et al., 2013).

Ethylcellulose is one of the most commonly used polymers for sustained release film coating (Melegari et al., 2016). Considering this polymer in a dry powder coating process, its high glass transition temperature (Tg) around 129–133 °C (Ethylcellulose Polymer technical Handbook, Dow Cellulosic, 2016) could represent an obstacle for the process execution. Coating formulations usually contain many additives, in addition to the polymer, that aid

* Corresponding author.
E-mail address: beatrice.albertini@unibo.it (B. Albertini).

http://dx.doi.org/10.1016/j.ijpharm.2016.11.054
0378-5173/

in processing, appearance and product performance (Felton et al., 2008). Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their permeability by the addition of hypromellose or a plasticizer. The amount and type of plasticizer in the film and the presence of other additives in the coating can significantly impact the film's mechanical properties. Ethylcellulose is compatible with numerous lipophilic plasticizers: dibutyl phthalate; diethyl phthalate; dibutyl sebacate; triethyl citrate; tributyl citrate; acetylated monoglyceride; acetyl tributyl citrate; triacetin; dimethyl phthalate; benzyl benzoate; butyl and glycol esters of fatty acids; refined mineral oils; oleic acid; stearic acid; stearyl alcohol; castor oil; corn oil; and camphor (Dahl, 2009).

The first studies on dry powder coating of pellets with ethylcellulose were performed in a fluidized bed coater using the liquid assisted method (Pearnchob and Bodmeier, 2003a, 2003b). The use of small amount of water or aqueous binder solution facilitated the adhesion of the polymer particles onto the pellets and their coalescence. Pearnchob and Bodmeier (2003a) used a mixture of the polymer with talc and an emulsion of the plasticizer in a 10% w/w HPMC binder solution to achieve the powder adhesion to the cores. The study evidenced that small polymer particle size promoted an easy film formation. Moreover, pellets coated with polymer powders required higher coating levels to obtain similar drug release patterns to pellets coated with organic polymer solutions and aqueous polymer dispersions. High plasticizer concentrations (40%) of acetylated monoglyceride and a thermal after-treatment (curing) at 80 °C for 24 h were necessary for the coalescence of the polymer particles and good film formation. Although ethylcellulose-coated pellets had an uneven surface, extended drug release could be obtained with coating level of 15% (Pearnchob and Bodmeier, 2003b). Alternatively, to reduce the coating temperature and the random deposition of the polymer particles on the core surface, pre-plasticized ethylcellulose with 20% w/w of medium chain triglycerides was investigated (Terebesi and Bodmeier, 2010). Pre-plasticized ethylcellulose was prepared by spray-drying aqueous ethylcellulose dispersions (Surelease® or Aquacoat®) or by hot melt extrusion/cryogenic grinding of plasticized ethylcellulose. In the latter case, the coating process was performed without the additional used of water and thermal impact. Smikalla et al. (2015) analyzed several liquid additives (isopropyl myristate, cocoylcaprylocaprate, triacetin, octyldodecanol, triethylcitrate, PEG 400 and glycerol) (30–50% w/w on the dry polymer) to lower the Tg of ethylcellulose and to enhance the adhesion of the powder to the cores during rotor-granulation in a fluid bed processor. Curing at 80 °C for three days and the addition of isopropyl myristate resulted in the highest coating efficiency.

In this study a different strategy of dry powder coating was studied for the application of functional ethylcellulose based-coating upon pellets using a high shear rotogranulator. In particular, a novel and single step approach, based on a combination of liquid assisted and thermal adhesion technology, was developed and both the formulation and the process-related parameters were fully investigated. In particular, the research first focused on development of the film formulation through the selection of suitable plasticizers and the characterization of free-films. The best coating formula on the basis of the minimum film forming temperature and film stability was investigated on placebo pellets using the dry powder coating process. This was specifically developed for the application of the coating formulation inside the rotogranulator. Once the feasibility of the process was ascertained, the suitability of the coating formulation was evaluated. In a follow—up study (part II), we assess the drug release properties of dry powder coated pellets loaded with caffeine.

2. Materials and methods

2.1. Materials

Ethylcellulose ETHOCEL® Standard E7 FP Premium (E7, mean particle dimension 5–15 μm, max 140 μm; viscosity range 6–8 mPa*s), ETHOCEL® Standard E10 FP Premium (E10, mean particle dimension 3–15 μm, max 100 μm; viscosity range 9–11 mPa*s) and ETHOCEL® Standard E20 Premium (E20, viscosity range 9–11 mPa*s) (ETHOCEL™ Ethylcellulose, 2016, Technical Bulletin) and Sugar spheres (Suglets®14/16 mesh size, 1180–1400 μm diameter), composed of sucrose and starch (batch n° DT 405540) were kindly donated by Colorcon Ltd (Dartford, Kent, UK).

The selected plasticizers had different lipid composition (mono/triglycerides or fatty acids) and thus differing for their melting point: Dynasan 114 (trimyristin, mp = 56 °C, Sasol, Witten, Germany), glycerylmonostearate (GMS, mp = 75 °C, Sigma-Aldrich, Milan, Italy), Myvatex (a blend of at least 90% of distilled monoglycerides, partially unsaturated, derived from soybean oil, mp = 72 °C, Prabo srl, Cremona, Italy) and Myverol 18-04 (distilled monoglycerides of saturated fatty acids, mainly glyceryl monostearate and glyceryl monopalmitate (mp = 74 °C), Prabo srl, Cremona, Italy); lauric acid (LA, dodecanoic acid, mp = 48 °C, Sigma-Aldrich, Milan, Italy, batch n° MKBQ4605 V); myristic acid (MA, tetradecanoic acid, mp = 58 °C, Fluka, Milan, Italy) and oleic acid (OA; *cis*-9-octadecanoic acid, mp = 13–14 °C, Carlo Erba, Milan, Italy, batch n° 3185E100). Lauric acid was both used as received (<500 μm) and sieved (<150 μm and <100 μm), while all the other materials were used as received.

Vinylpyrrolidone-vinylacetate copolymer (Kollidon VA 64 Fine, Copovidone Ph. Eur., batch n° 61611468E0, particle size >90%< 50 μm) was kindly donated by BASF (Ludwigshafen, Germany). Talc was supplied by ACEF SpA (Piacenza, Italy). Red Sudan III (fat soluble dye) was supplied by Sigma-Aldrich, Milan, Italy.

2.2. Methods

2.2.1. Pre formulation study: screening of polymer and plasticizers

A pre-formulation study based on binary physical mixtures was carried out through differential scanning calorimeter (DSC) measurements. The thermal properties of raw ethylcellulose and of the samples were characterized using a Perkin-Elmer DSC 6 (Perkin-Elmer, Beaconsfield, UK) equipped with Pyris Software. Samples, weighting 8–12 mg, were put in aluminium pans and heated from 25 °C to 180 °C at a scanning rate of 10 °C/min under a nitrogen flow rate of 20 mL/min. The glass transition temperature (T_g) was calculated setting first the limits of the starting and the end points of the thermal event. Then the transition point was calculated using the Half Cp extrapolated, that reports the point between the limits at which the slope of the curve changes from increasing to decreasing or vice versa. Each analysis was carried out in duplicate experiments and the mean of the calculated Tg and the SD were reported.

The analysed samples were raw ethylcellulose and powder mixtures containing several types of plasticizers at different concentrations to evaluate their efficiency in lowering the T_g of the coating blend. In particular, three types of ethylcellulose (E7, E10 and E20), which essentially differed in molecular weight and viscosity degree, were used. The screening of the plasticizer was conducted by preparing six physical mixtures with E7 and all plasticizers listed in Table 1. The best plasticizer of E7 was then used with E10 and E20.