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Effect of annealing time and addition of lactose on release of a model substance from Eudragit® RS coated pellets produced by a fluidized bed coater

Ulrich M. Heckötter[a,b], *Anette Larsson*[b], *Pornsak Sriamornsak*[a,c], *Mont Kumpugdee-Vollrath*[a,*]

[a] *Department of Pharmaceutical and Chemical Engineering, University of Applied Sciences Berlin, Luxemburger Straße 10, D-13353 Berlin, Germany*

[b] *Department of Chemical and Biological Engineering, Chalmers University of Technology, S-41296 Gothenburg, Sweden*

[c] *Department of Pharmaceutical Technology, and Pharmaceutical Biopolymer Group (PBiG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand*

ABSTRACT

The aim of this study was to investigate the effects of annealing time and addition of lactose in coating liquid formulations on the release of a model substance, methylene blue (MB), from pellets coated with Eudragit® RS 30 D. The microcrystalline cellulose pellets were layered with MB before coating with aqueous dispersions of Eudragit® RS 30 D using a Wurster-type fluidized bed coater. The coating processes and conditions were validated and optimized before the final coating. The uncoated and coated pellets were characterized for their size, MB content, morphology and MB release. The results demonstrated that a stable coating process can be developed to produce repeatable batches of pellets. The film thickness was calculated and found to be similar to those observed from scanning electron microscope. The increased annealing time led to a more coherent film. The drug release was found to vary depending on the duration of annealing time and the addition of lactose. Addition of lactose gave a faster MB release and without any initial lag period in the release profile whereas the increased annealing time slowed down the MB release and increased the lag period.

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1. Introduction

Pharmaceutical pellets are used in controlled-release oral solid dosage forms and provide advantages over monolithic single-dose units such as tablets. For instance, the risk of dose dumping is reduced, and mixtures of pellets of different release patterns can be used to control drug delivery with time (Chopra et al., 2002). Coating of pellets can be applied in order to modify colour, give protection, cover taste or create a modified release properties. Polymeric film coatings have been used in pharmaceutical products for many years (Aulton, 2002). Nowadays, the film coatings can be mainly applied on the products by using two different starting materials; film coating materials dissolved in organic solvents or film coating materials as aqueous dispersions (latex). The latter is of interest and increasing importance due to the environmental concern, as well as safty and economic reasons; there has been a trend during the past 30 years to avoid using volatile organic compounds in all types of coating and use aqueous dispersion formulations as an alternative (Fukumori, 1994; McGinity, 1997).

Aqueous film coating dispersions generally consist of polymeric colloidal particles, a plasticizer and an antiadherant. Most polymers used for the film coating of pellets and tablets are brittle at room temperature and require the use of plasticizers to improve their handling and processing (Wu and McGinity, 2001). The most widely used aqueous polymer dispersions for sustained release application are either

* Corresponding author. Tel.: +49 30 4504 2239; fax: +49 30 4504 2813.
E-mail address: vollrath@beuth-hochschule.de (M. Kumpugdee-Vollrath).
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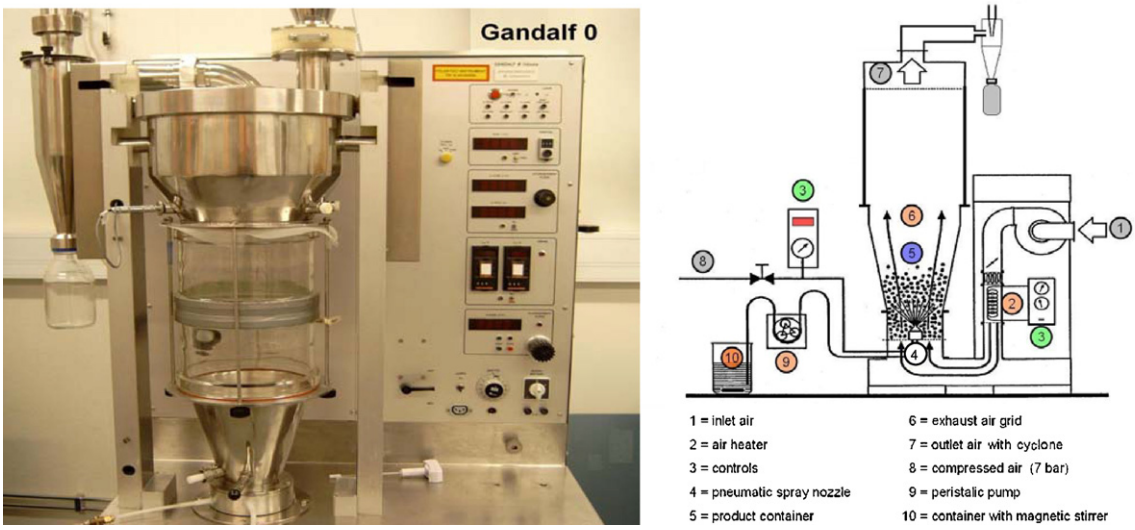

Fig. 1 – Fluidized bed coating equipment, Gandalf 0 (AstraZeneca, Sweden).

ethylcellulose-based or acrylate-based products. Eudragit® RS 30 D, 30% (w/w) aqueous dispersion, is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. It can be used as a pH independent polymer for sustained release or time-controlled release formulations. Eudragit® RS are extensively used in pharmaceutical products, e.g., for sustained release formulations (Wu and McGinity, 2001; Kibria et al., 2010) and targeted release to the human gastrointestinal tract (Sriamornsak et al., 2003).

Fluidized-bed technology has been widely used for coating of pharmaceutical products. Due to its highly efficient drying capacity, this technique seems to be ideal for coating beads, pellets and particles which tend to agglomerate in a wet condition. It was reported that the coatings can be reproducibly performed by this technique with minimal defects of products. Therefore this technique was preferred for many formulations (Rhodes and Porter, 1998). The fundamental principle behind fluidized-bed coating in general and the Wurster technique in particular is to suspend materials in an upward-moving column of warm air during the coating process (Wurster, 1990). The 'Gandalf 0', a Wurster-type fluidized bed coating equipment, provides a fluidization air flow with possibilities of varying the air volume rate and temperature of the inlet air; the coating liquid is applied by using a pneumatic atomization nozzle ("Schlick" nozzle) where the liquid addition rate, the atomizer pressure and air flow can be regulated. Many parameters will affect film formation, and are highly dependent on the characteristics of a given polymer. Therefore, it is necessary to investigate the processing conditions during product development. Because of the possibility to vary the coating parameters, a special control of these parameters with a calibration is necessary. The combination of parameters should be carefully selected in order to optimize the process, as many factors can affect the fluidized bed process (Bodmeier and Paeratakul, 1994).

Once sprayed onto the surface of tablets or pellets, the droplets of the aqueous polymer dispersion form a thin aqueous film. Due to water evaporation, the dispersed polymer particles approach each other and become more concentrated and then closely packed. Upon further water evaporation, the particles deform due to capillary pressure effects and coalesce to form a continuous film (Chevalier et al., 1992; Keshikawa and Nakagami, 1994; Dobler and Holl, 1996; Steward et al., 2000). In practice, it is difficult to assure complete film formation during coating. Therefore, a thermal post-treatment (curing or annealing step) is required to enhance the degree of polymer particle coalescence in most cases (Yang et al., 2010). Annealing time is one of the crucial parameters in this processing step which need to be optimized. A number of studies have been addressed the importance of the curing step for the drug release rate and storage stability (e.g., Keshikawa and Nakagami, 1994; Yang et al., 2010). However, the impact of the addition of lactose as a pore former and the importance of annealing time have not been studied; especially with the Eudragit® RS film coatings. Therefore, the aim of this study was to investigate the effects of annealing time and addition of lactose on the release of a highly water soluble substance, methylene blue (MB), from the pellets coated with Eudragit® RS 30 D. The characteristics and morphology of the coated pellets were also examined.

2. Materials and methods

2.1. *Materials*

Microcrystalline cellulose pellets (Cellets® 700, batch number 02105001, referred as MCC pellets), which the mode of size distribution is in the size range of 710–1000 μm, were a gift from Syntapharm GmbH (Mülheim an der Ruhr, Germany). Eudragit® RS 30 D (30%, w/w aqueous dispersion, batch number G040718108) was a gift from Degussa Röhm Pharma Polymer (Darmstadt, Germany). Methylene blue (batch number 125068244606135, referred as MB) and triethyl citrate (batch number 12280915405122) were purchased from Sigma–Aldrich Laborchemikalien GmbH (Seelze, Germany). Polysorbate 80 (Tween® 80) and lactose were purchased from BDH Laboratory Supplies (Poole, UK). Talcum was given by Astra Zeneca (Mölndal, Sweden). All other chemicals were of reagent or food grade and used as supplied. Distilled water was used throughout all experiments.

2.2. *Preparation of MB-loaded pellets*

In this study, MB was used as a model substance as the leakage and release from the pellets could be observed very easily. The MB solution was layered on the MCC pellets using a pilot scale

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