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Research paper

Curing mechanism of flexible aqueous polymeric coatings

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ABSTRACT

The objective of this study was to explain curing phenomena for pellets coated with a flexible polymeric coating based on poly(vinyl acetate) (Kollicoat® SR 30D) with regard to the effect of starter cores, thickness of drug layer, adhesion of coating to drug-layered-cores as well as coating properties. In addition, appropriate approaches to eliminate the curing effect were identified. Sugar or MCC cores were layered with the model drugs carbamazepine, theophylline, propranolol HCl, tramadol HCl and metoprolol HCl using HPMC (5 or 25% w/w, based on drug) as a binder. Drug-layered pellets were coated with Kollicoat® SR 30D in a fluidized bed coater using TEC (10% w/w) as plasticizer and talc (35–100% w/w) as anti-tacking agent. Drug release, pellet properties (morphology, water uptake-weight loss and osmolality) and adhesion of the coating to the drug layer were investigated as a function of curing at 60 °C or 60 °C/75% RH for 24 h. The film formation of the aqueous dispersion of Kollicoat® SR 30D was complete, and therefore, a strong curing effect (decrease in drug release) at elevated temperature and humidity (60 °C/75% RH) could not be explained by the well-known hydroplasticization and the further gradual coalescence of the colloidal polymer particles. According to the provided mechanistic explanation, the observed curing effect was associated with (1) high flexibility of coating, (2) adhesion between coating and drug layer, (3) water retaining properties of the drug layer, and (4) osmotically active cores. Unwanted curing effects could be minimized/eliminated by the addition of talc or/and pore-forming water soluble polymers in the coating, increasing binder amount or applying an intermediate coating, by increasing the thickness of drug layer or using non-osmotic cores. A new insight into curing phenomena mainly associated with the adhesion between drug layer and coating was provided. Appropriate approaches to avoid unwanted curing effect were identified.

1. Introduction

The drug release mechanism from polymer-coated reservoir systems is generally understood as a series of three rate-limiting steps: permeation of water across the coating, dissolution of the drug core and finally drug diffusion through the coating into the release medium [1,2]. The last step is understood as drug diffusion through the intact film coatings and/or water-filled cracks. Since no permeation of water-soluble substrates occurred through monolithic free films, it was assumed that drug was released primarily through channels or pores considered as artefacts of the coating process or created upon increased osmotic pressure during drug release [2,3]. In the case of flexible aqueous polymeric coatings (based on Eudragit® NE 30D), drug release could also occur through the intact but elongated/stretched coating [2].

The phenomenon of decreased drug release upon thermal after-treatment (curing effect) is well-known for the commercially available polymer dispersions (e.g., Eudragit® RS 30D, Eudragit® RL 30D and Aquacoat® ECD). Curing is often used to obtain complete film formation and stable release profiles during long term storage [4]. However, pellet curing at elevated temperature and ambient relative humidity not always alters the coatings as shown for HPMCAS film coatings [5]. Humidity treatment led to a decrease in the drug release rate even at ambient temperature due to the plasticizing effect of water. The most pronounced curing effect was observed by the combination of both elevated temperature and humidity during curing [5].

Changes in the acrylic polymer film were attributed to the hydroplasticization effect, whereby the fracture behaviour of coated beads stored at 0% RH changed to ductile behaviour following equilibration at 84% RH [6]. Improvement of the coalescence of

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polymeric particles was confirmed by the irreversibility of changes in the film properties and drug release from the pellets coated with aqueous dispersion of cellulose acetate phthalate (Aquacoat® CPD). The extent of coalescence via heat/humidity curing was dependent on the curing temperature, % humidity, curing time and the coating temperature [7]. In addition to moisture, plasticizers play a significant role during heat/humidity curing of beads coated with Aquacoat® CPD since the process was not effective without plasticizers. Despite the difference in solubility, diethyl phthalate (DEP) and triethyl citrate (TEC) were both effective plasticizers facilitating the heat-humidity curing process to improve the film coalescence [8]. Film formation during coating/curing was also improved by the addition of PVA-PEG graft copolymer (e.g., 15% w/w) to Aquacoat® ECD in order to overcome the instability of theophylline release from the coated pellets upon storage at elevated humidity. This effect was explained by the trapping of water within the polymeric network by hydrophilic PVA-PEG graft copolymer [9].

Exposure of coated solids to various temperatures or relative humidities can affect polymer adhesion attributed to increased internal stresses in the polymeric films [10] or to the swelling-induced internal stresses at the film-tablet interface [11]. Storage of tablets at high humidities can also result in cohesive failure due to the weakening of tablets by the sorption of moisture from the environment [12].

An aqueous colloidal polyvinyl acetate dispersion (Kollicoat® SR 30D) was characterized by excellent film forming and mechanical properties and presents a good alternative to the well established commercial cellulosic and acrylate based aqueous dispersions [13–15]. Kollicoat® SR 30D has been investigated as a coating material to achieve sustained drug release [16], as a matrix former by spray drying of buspirone HCl/Kollicoat® SR 30D [17] or compression of coated granules [18] as well as to prevent the bitter taste and side effects of orally disintegrating tablets containing ibuprofen [19]. The high flexibility of the Kollicoat® SR 30D coatings in the wet stage was used to formulate expanding carbon dioxide developing systems [20,21].

Propranolol HCl release from Kollicoat® SR 30D coated pellets was independent of the coating product temperature (30 or 40 °C) and curing at 60 °C due to its low minimum film forming temperature (MFT = 18 °C) [14]. In addition, no significant changes in drug release were observed upon storage at 25 °C/60% RH for diphenhydramine HCl pellets coated with Kollicoat® SR 30D. However, drug release decreased upon storage at 40 °C/75% RH [22].

The objective of this study was to investigate and to mechanistically understand curing phenomena of Kollicoat® SR 30D coatings and to provide appropriate approaches to eliminate them.

2. Materials and methods

2.1. Materials

Aqueous dispersion of poly(vinyl acetate) (Kollicoat® SR 30D, BASF SE, Ludwigshafen, Germany), triethyl citrate (TEC, Morflex, Greensboro, NC, USA), hydroxypropyl methylcellulose (HPMC, Pharmacoat® 606, Shin-Etsu Chemical, Tokyo, Japan), sugar spheres (Suglets® 710–850 μm, NP Pharma, Bazainville, France), microcrystalline cellulose cores (MCC, Celphere® 507, Asahi Kasai Chemical, Tokyo, Japan), carbamazepine (Cs = 0.2 mg/ml), theophylline (Cs = 10 mg/ml), propranolol HCl (Cs = 212 mg/ml), tramadol HCl (Cs = 500 mg/ml) and metoprolol tartrate (Cs = >1000 mg/ml) (BASF SE, Ludwigshafen, Germany), talc (Luzenac Europe, Toulouse, France), Ludipress® (BASF, Ludwigshafen, Germany), colloidal silica (Aerosil® 200, Evonik Degussa GmbH, Frankfurt am Main, Germany), sodium chloride.

2.2. Preparation of drug-layered pellets

The model drugs were layered onto sugar or MCC cores using HPMC as a binder (5 or 25% w/w, based on drug). The drug layering solution based on ethanol:water mixture (60:40) with a solid content of 15% w/w was sprayed onto cores in a fluidized bed coater (Glatt GPCG-1, Glatt GmbH, Binzen, Germany) to achieve a 2, 5, 10, 20, 30 and 50% w/w weight gain. Optionally, the drug layered pellets were sub-coated using 7.5% w/w solution of HPMC to attain a weight gain of 10% w/w.

The layering conditions were: batch size = 900 g, inlet temperature = 52 °C, product temperature = 40 °C, airflow = 100 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 8.5 g/min, final drying at 40 °C for 15 min.

2.3. Coating of the drug-layered pellets

The drug layered pellets were coated using the aqueous dispersion of Kollicoat® SR 30D (15% w/v solids content) in a fluidized bed coater (Glatt GPCG-1, Glatt GmbH, Binzen, Germany) to obtain the pre-determined weight gain (20% w/w, based on dry polymer mass). The dispersion was plasticized with 10% w/w triethyl citrate (TEC) (based on dry polymer mass) and talc 35–100% w/w (based on dry polymer mass) was used as anti-tacking agent. Optionally, HPMC 7.5% w/w (based on dry polymer mass) was added as a pore-former. The coating conditions were: batch size = 900 g, inlet temperature = 36 °C, product temperature = 30 °C, airflow = 72 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 2 bar, spray rate = 7.8 g/min, final drying at 40 °C for 10 min. After coating, 0.5% w/w of colloidal silica (Aerosil® 200) was mixed to pellets to avoid sticking. The pellets were cured at 60 °C or 60 °C/75% RH for 24 h and then were equilibrated in a desiccator for 48 h.

Unless otherwise mentioned, the drug-layered cores were coated with 20% w/w of Kollicoat® SR 30D using 10% w/w TEC (plasticizer) and 35% w/w talc (anti-tacking agent).

2.4. Preparation of isolated films

The films were prepared by spraying a 15% w/v aqueous dispersion of Kollicoat® SR 30D, pre-plasticized with 10% w/w triethyl citrate (TEC) (based on dry polymer mass), using an Airbrush with a nozzle diameter of 0.75 mm (Paasche Chicago, IL, USA) onto Teflon plates (14 × 14 cm^2). Optionally, the films (50–100 μm thick) were cured at 60 °C or 60 °C/75% RH for 24 h and then stored in a desiccator for 48 h until further use.

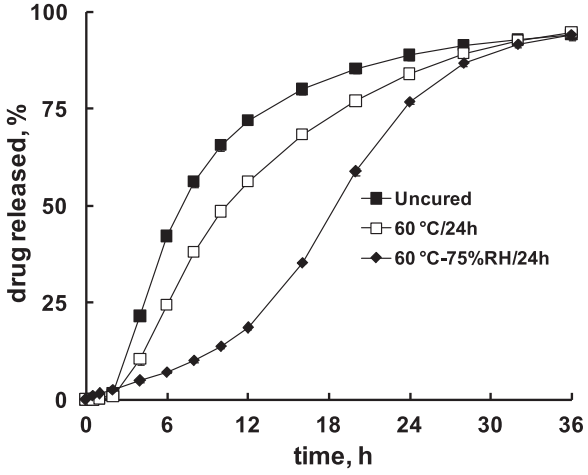

Fig. 1. Effect of curing on drug release in 0.01 N HCl of coated pellets based on sugar cores loaded with 10% propranolol HCl/(HPMC 5%).