Journal of Controlled Release 135 (2009) 71–79

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Prediction of drug release from ethylcellulose coated pellets

S. Muschert [a], F. Siepmann [a], B. Leclercq [b], B. Carlin [c], J. Siepmann [a,*]

[a] College of Pharmacy, JE 2491, University of Lille, 3 Rue du Professeur Laguesse, 59006 Lille, France
[b] FMC BioPolymer, Avenue Mounier 83, 1200 Brussels, Belgium
[c] FMC BioPolymer, US Route 1 & Plainsboro Road, Princeton, NJ 08543, USA

ARTICLE INFO

Article history:
Received 16 October 2008
Accepted 6 December 2008
Available online 24 December 2008

Keywords:
Drug release mechanism
Ethylcellulose
Mathematical modeling
Film coating
Pellet

ABSTRACT

The aim of this study was to elucidate the underlying drug release mechanisms in pellets coated with aqueous ethylcellulose dispersion, providing long term stable drug release profiles and containing different types of starter cores. The systems were thoroughly characterized using mechanical analysis; the sensitivity of drug release to the osmolality of the release medium was measured; scanning electron microscopy and optical macroscopy were used to monitor the pellets' morphology and dimensions upon exposure to different media, and drug release was measured from single and ensembles of pellets as well as from thin, free films. All experimental results indicate that diltiazem HCl release from pellets coated with ethylcellulose containing small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer is primarily controlled by drug diffusion through the intact polymeric membranes, irrespective of the type of starter core (consisting of microcrystalline cellulose or sugar, optionally coated with ethylcellulose). Importantly, the apparent diffusion coefficient of the drug in the macromolecular networks could easily be determined with thin free films and successfully be used to quantitatively predict the release rate from coated pellets. Thus, based on this knowledge and using the presented mathematical theories the development of new/ optimization of existing controlled drug delivery systems of this type can be significantly facilitated.

1. Introduction

Coated pellets are frequently used for oral controlled drug delivery [1–5]. Compared to coated tablets and capsules they avoid the all-or-nothing effect of single unit dosage forms and provide less variable transit times within the gastro intestinal tract (GIT), together with a facilitated spreading of the administered drug dose within the contents of the GIT. Compared to controlled release matrix pellets and mini-tablets, generally higher drug loadings can be achieved. Ethylcellulose is a highly suitable polymer for controlled release pellet coatings, since it is nontoxic, nonallergenic, nonirritant and a good film former. This polymer can be applied from organic solutions or aqueous dispersions [6–8]. The use of aqueous dispersions avoids toxicity and environmental concerns associated with organic solvents and decreasing the viscosity of the coating formulation (at similar polymer contents) compared to organic solutions. Thus, higher polymer contents can be applied, resulting in shorter processing times. However, long term stability might be difficult to achieve, in particular upon storage under stress conditions (elevated temperature and relative humidity): If the polymer particles are not completely coalesced, the release rate might decrease with time due to ongoing film formation [9–11]. It has recently been shown that the addition of small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer) to aqueous ethylcellulose dispersion can effectively overcome this restriction [12–15]. The presence of this hydrophilic compound is likely to trap water within the film coating during coating and curing, resulting in improved film formation (water acting as a plasticizer for ethylcellulose and being mandatory for the capillary forces driving the polymer particles together).

However, yet it is unclear which mechanisms control drug release from such pellets. In addition, it is unknown how the type of pellet starter core (consisting for example of sugar or microcrystalline cellulose) and the osmolality of the release medium affect the resulting drug release kinetics. Different types of release mechanisms have been reported in the literature for polymer coated solid dosage forms [1,16–18], including for instance drug diffusion through intact macromolecular networks, crack formation and subsequent drug release through water-filled pores, drug dissolution, water penetration into the pellets, polymer swelling and/or (partial) dissolution, and osmotic effects generated by the pellet core. The mechanical stability of the film coatings and the hydrostatic pressure generated upon water penetration into the pellet core determine whether or not crack formation in the polymeric membranes occurs. In general, drug release through water-filled cracks is much more rapid than through the intact polymer membrane. Depending on the complexity of the involved mass transport mechanisms, more or less straightforward mathematical theories have been proposed to quantify drug release from coated dosage forms [19–23]. For instance, Axelsson and co-

* Corresponding author. Tel.: +33 3 20964708; fax: +33 3 20964942.
E-mail address: juergen.siepmann@univ-lille2.fr (J. Siepmann).

0168-3659/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2008.12.003

workers proposed interesting theories taking into account internal and external mass transfer resistances in addition to drug diffusion through the film coating, as well as effects of the osmotic pressure of the pellet core on the resulting drug release kinetics from pellets coated with organic ethylcellulose solutions. However, the film formation mechanism from aqueous polymer dispersions is fundamentally different and the properties of the resulting polymeric membranes can substantially differ, despite of identical coating compositions [8]. Yet, it is unclear which are the dominant mass transport mechanisms from pellets coated with aqueous ethylcellulose dispersion and how drug release can be easily predicted based on a few, straightforward experiments. Ideally, thin free films might serve as surrogates for real film coatings surrounding the pellets, because they are much easier to prepare.

The aim of this study was to better understand the underlying drug release mechanisms from pellets coated with aqueous ethylcellulose dispersion providing long term stable drug release profiles and to present a mathematical theory that allows for quantitative predictions of the resulting drug release kinetics based on only a few, simple experimental trials with thin, free films. The practical benefit of this model is to facilitate the development of new/ optimization of existing controlled drug delivery systems of this type, minimizing the number of required labor-intensive coating trials.

2. Materials

Diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France), sugar cores (sugar spheres NF, 710–850 μm; NP Pharm, Bazainville, France), microcrystalline cellulose cores (MCC cores, Celpheres CP-708, 710–850 μm; Asahi Kasei, Tokyo, Japan), Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC Biopolymer, Philadelphia, USA), poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer (PVA-PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany), triethyl citrate (TEC; Morflex, Greensboro, USA), hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK), saccharose (Beghin Say, Thuleries, France), sodium chloride (NaCl; Fisher Bioblock Scientific, Illkirch, France).

3. Experimental methods

3.1. Preparation of free films

Thin polymeric films were prepared by casting blends of aqueous ethylcellulose dispersion (plasticized with 25% w/w TEC, based on the ethylcellulose content; overnight stirring) and aqueous PVA-PEG graft copolymer solution (6.6% w/w). The mixtures were stirred for 30 min prior to casting into Teflon molds and subsequent controlled drying for 24 h at 60 °C in an oven. Drug loaded films were prepared accordingly, adding 1.3% w/w drug (referred to the dry film mass) to the aqueous blend. Under these conditions the drug was dissolved in the film.

3.2. Characterization of free films

The *thickness* of the films (around 400 μm) was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

The *mechanical properties* of the films were measured using a texture analyzer (TA.XT Plus, Stable Micro Systems, Surrey, UK) before and after exposure to 0.1 N HCl, optionally saturated with saccharose. Film pieces of 7×7 cm were placed into 250 mL plastic flasks filled with 200 mL pre-heated medium and agitated in a horizontal shaker (80 rpm, 37 °C; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). After pre-determined time points, samples were withdrawn and mounted on a film holder (n=6). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg), and driven downward with a cross-head speed of 0.1 mm/s to the center of the film holder's hole. Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\text{puncture strength} = \frac{F}{A} \tag{1}$$

Where F is the load required to puncture the film and A the cross-sectional area of the edge of the film located in the path.

$$\%\ \text{elongation at break} = \frac{\sqrt{R^2 + D^2} - R}{R} \cdot 100\% \tag{2}$$

Here, R denotes the radius of the film exposed in the cylindrical hole of the holder and D the displacement.

$$\text{energy at break per unit volume} = \frac{\text{AUC}}{V} \tag{3}$$

Where AUC is the area under the load versus displacement curve and V the volume of the film located in the die cavity of the film holder.

Drug release from thin free films was measured by placing 2×2 cm specimen into 100 mL plastic flasks filled with 80 mL pre-heated 0.1 N HCl or phosphate buffer pH 7.4 (USP 30) followed by horizontal shaking (37 °C, 80 rpm; GFL 3033; n=3). At predetermined time points, 3 mL samples were withdrawn (replaced with fresh medium) and analyzed UV-spectrophotometrically (λ=236.9 nm in 0.1 N HCl and λ=237.4 nm in phosphate buffer pH 7.4; UV-1650PC, Shimadzu, Champs-sur-Marne, France).

The *partition coefficient* of the drug between the polymeric film and the release medium at 37 °C was determined by placing film pieces of 2.5×2.5 cm in preheated 0.1 N HCl and phosphate buffer pH 7.4 (USP 30), with an excess of diltiazem HCl, and subsequent agitation in a horizontal shaker (80 rpm; GFL 3033; n=3) until equilibrium was reached. The saturation concentration of the drug in the bulk fluids was determined UV-spectrophotometrically as described above. The drug concentration in the saturated polymeric films was determined as follows: The film specimen were withdrawn from the release medium, excess water removed, weighed, and the diltiazem HCl content determined UV-spectrophotometrically upon dissolution in ethanol (λ=242 nm, UV-1650PC).

3.3. Preparation of coated pellets

3.3.1. Sealed sugar cores

Sugar starter cores were coated with aqueous ethylcellulose dispersion (plasticized with 25% w/w TEC, overnight stirring) in a fluidized bed coater equipped with a Wurster insert (Strea 1, Niro Inc.; Aeromatic-Fielder, Bubendorf, Switzerland) until a coating level of 15% w/w was achieved. The process parameters were as follows: inlet temperature=38 °C, product temperature=38±1 °C, spray rate=2–3 g/min, atomization pressure=1.2 bar, nozzle diameter=1.2 mm.

3.3.2. Drug layered starter cores

Sugar cores, MCC cores and sealed sugar cores were coated with an aqueous solution of diltiazem HCl (18.2% w/w) and HPMC (0.9% w/w) in a fluidized bed coater (Strea 1, Wurster insert). The process parameters were as follows: inlet temperature=40 °C, product temperature=40±2 °C, spray rate=1–3 g/min, atomization pressure=1.2 bar, nozzle diameter=1.2 mm. The final drug loading was 10% w/w.

3.3.3. Controlled release pellets

The drug layered sugar, MCC and sealed sugar cores were coated with aqueous ethylcellulose dispersion containing 10% (w/w) PVA-PEG graft copolymer in a fluidized bed coater (Strea 1, Wurster insert)