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The Influence of Hydrophilic Pore Formers on Dipyridamole Release from Aqueous Ethylcellulose Film-Coated Pellets

Dasha Palmer, Hue Vuong, Marina Levina and Ali R.Rajabi-Siahboomi
Colorcon, Dartford, United Kingdom

Introduction

There is growing interest in extended release (ER) drug delivery systems, especially in the design of challenging formulations such as multi-particulate (MP) systems containing poorly water-soluble actives.

After ingestion, MP dosage forms move more evenly through the gastro-intestinal tract than monolithic dosage forms, leading to a reduced risk of local side-effects and dose dumping[1]. Ethylcellulose (EC) is a water-insoluble polymer, widely used in organic and aqueous film coating applications to achieve extended drug release[2].

The objective of this work was to study the effect of incorporating water-soluble polyvinyl alcohol (PVA) and polyethylene glycol (PEG) as a pore former into aqueous EC (Surelease®, Colorcon) films, and how they influence dipryridamole release from the pellets.

Methodology

Drug Layering
Dipyridamole (Aceto Corporation, USA) was dispersed in 8% w/w aqueous Opadry® OY-29020 Clear (Colorcon, USA) solution and mixed for 45 minutes using a low-shear propeller blender (IKA Labortechnik, Germany). The prepared solution was then screened through a 250 µm sieve. Drug was layered onto a 1.2 kg batch of non-pareils (NPTAB 650, NP Pharm, France) in a Glatt GPCG-1.1 (Glatt GmbH, Germany) fluid-bed fitted with a Würster column and 1-mm Schlick spraying nozzle.

Surelease® and Surelease®/Pore Former Coating
Drug-layered pellets were coated with Surelease® E-7-19040 to 2.5, 3.5, 5, 7.5, 10 and 12% weight gain (WG). Drug-layered beads were also coated with dispersions containing various ratios (95:5, 90:10, 85:15, 80:20, 70:30) of Surelease® and pore former (PVA or 83:17 PVA/PEG 3350) to 12% WG (Table 1). All coating trials were performed using dispersion at 15% w/w solids level.

Dispersion Viscosity Measurement
Viscosity measurements of Surelease® dispersion at 15% solids containing 10, 20 and 30% (w/w, with respect to dry powder) of pore formers were carried out using a digital Rheometer (DV-III+rheometer, Brookfield Engineering Laboratories, USA).

Table 1. Surelease®/Pore Former Dispersion (15% solids, 1 kg) Preparation

Surelease®: Pore Former Ratio	Amount of individual ingredients added (g)		
	Surelease® dispersion*	Pore former solution**	Water
95:5	570	50	380
90:10	540	100	360
85:15	510	150	340
80:20	480	200	320
70:30	420	300	280

* Surelease® dispersion at 25% solids ** Pore former solution at 15% solids

Optical & Scanning Electron Microscopy Study
Appearance of pellets post drug layering and Surelease®/pore former coating was inspected using a light microscope (Olympus Optical Company, Japan) fitted with a digital camera and scanning electron microscope (JEOL, Japan).

Dissolution Testing
Drug release was measured from 1 gram of coated beads in a Sotax (Switzerland) dissolution bath in accordance with the USP monograph for "Dipyridamole tablets", but using Apparatus I (baskets) at 50 rpm. Dissolution medium was 0.1N HCl at 37.0±0.5°C. A dual beam UV/VIS spectrophotometer (Lambda 25, Perkin Elmer Instruments, UK) was used for the detection of dipyridamole at a wavelength of 283 nm. The mean of three determinations is reported. The dissolution profile comparison was carried out using a similarity factor (f_2). An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar.[4, 5]

Results and Discussions

It was found that upon addition of pore former (up to 30% w/w) to Surelease® the viscosity of the final dispersion increased, from less than 50 mPa-s to 420 and 350 mPa-s for PVA and PVA/PEG, respectively (Figure 1). Therefore 15% solids was considered to be an optimum dispersion concentration for conducting coating trials. Drug-layered and ER film-coated pellets exhibited good appearance, showing no visually or microscopically detected defects in the coating (Figure 2).

Figure 1. Viscosity Profiles of Surelease® Dispersion (15% solids) Containing PVA or PVA/PEG

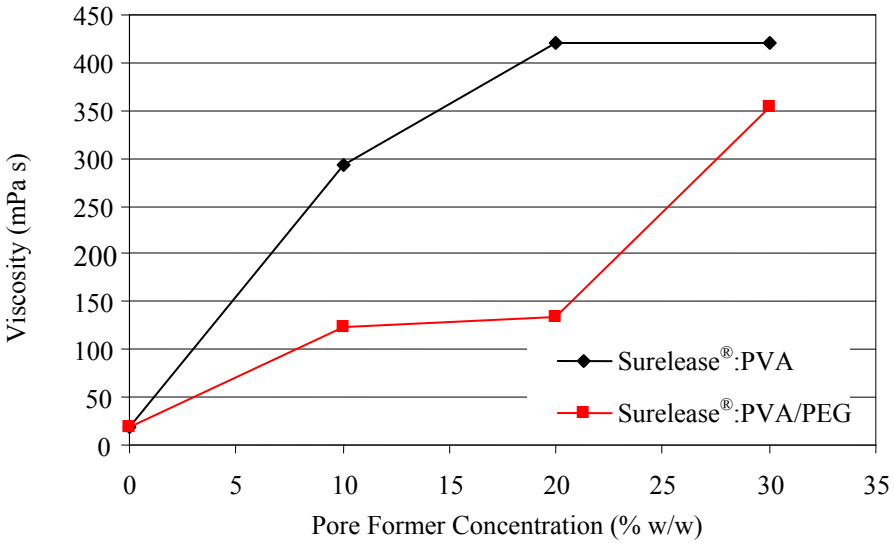
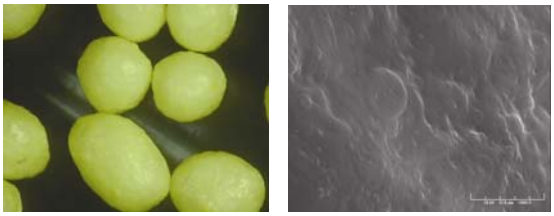


Figure 2. Drug-layered Pellets Coated with Surelease® or Surelease®/Pore Former (a) x50, (b) x1000 magnification



Dipyridamole dissolution data was highly reproducible with standard deviations of less than 2% (n=3). Figure 3 shows that the rate of drug release from Surelease® coated pellets decreased progressively as the coating level increased. At 12% WG only 20% of the drug was dissolved after 8 hours. Additionally, a lag time developed as the coating level exceeded 5% WG.

The inclusion of pore-formers into the EC film increased the dipyridamole release rate. For samples containing 20% w/w or more of the pore-former, approximately 90% of the drug was dissolved after 8 hours, compared to only 20% released from the Surelease® film (Figure 4). The enhanced dissolution rate was probably due to an increased permeability of the barrier membrane.

Inclusion of PEG with PVA in Surelease® did not significantly change the drug release compared to the ER film with PVA only. This was confirmed by the *f*2 values being greater than 50 (Table 2).

Figure 3. Dipyridamole Dissolution from Surelease® Coated Pellets

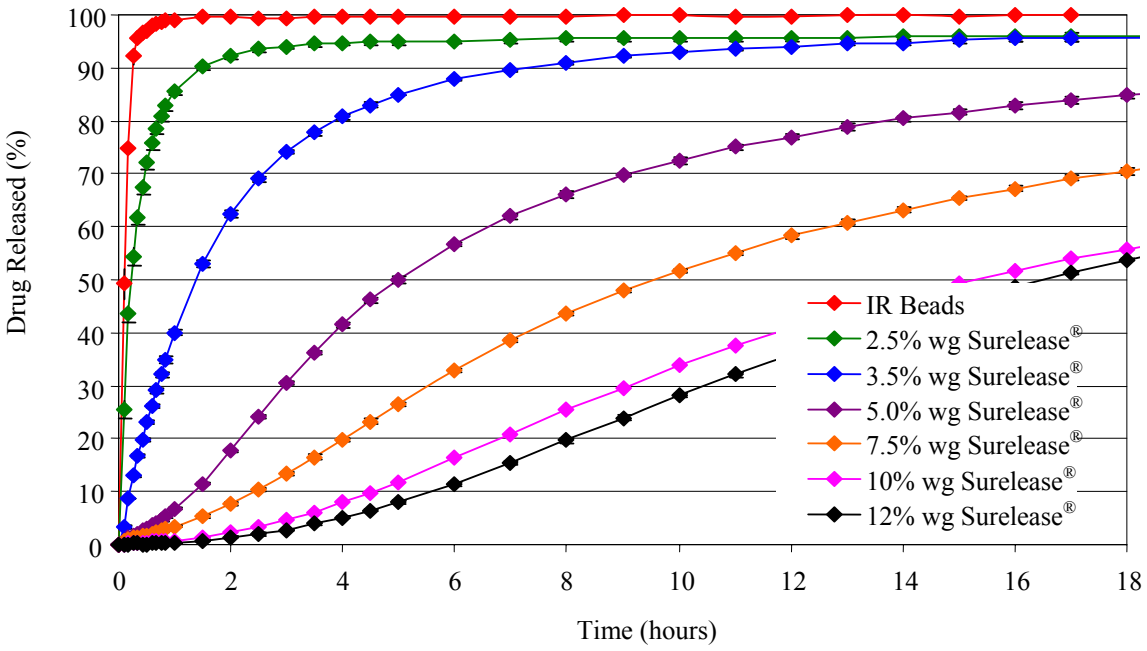


Figure 4. Dipyridamole Dissolution from Pellets Coated with Surelease® Containing PVA or PVA/PEG

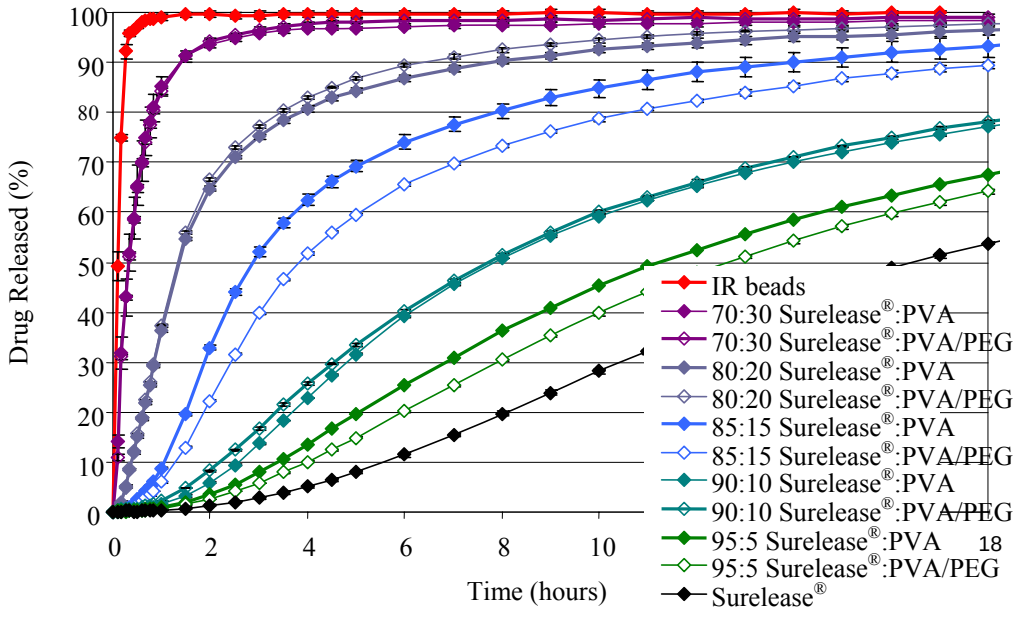


Table 2. f_2 Values for Dissolution Profiles when Using PVA or PVA/PEG as a Pore Former in Surelease®

Pore former concentration in Surelease® (% w/w)	*f*2 values
5	70
10	88
15	59
20	89
30	99

It was found that at higher pore former concentrations (i.e. 30%) the inclusion of PEG in the Surelease® dispersion resulted in reduced tackiness during coating, compared to when PVA alone was used, thus allowing a reduction in required coating process time. The results of this study confirm previously published data[6] on de-tackifying properties of PEG, when used in combination with PVA.

Conclusions

- It has been shown that incorporation of PVA or PVA/PEG at various concentrations (5, 10, 15, 20 and 30% w/w) into Surelease® E-7-19040 (aqueous ethylcellulose dispersion) film can be used to modulate release of a poorly water-soluble drug, dipyridamole.
- An increase in the amount of pore former added to the ER film resulted in an increase in rate of drug release. Inclusion of PEG with PVA in Surelease® did not change the drug release compared to the ER film where PVA only was used as a pore former.
- The inclusion of PEG into the Surelease® dispersion containing PVA resulted in a reduced tackiness during coating compared to when PVA alone was used. This result allowed a reduction in coating process time.

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World Headquarters
Colorcon
415 Moyer Blvd., P.O. Box 24, West Point, PA 19486-0024
Tel: 215-699-7733 Fax: 215-661-2605 Web Site @http://www.colorcon.com E.mail: modified_release@colorcon.com

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