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The Effect of Hypromellose as a Pore-Former on Drug Release from Aqueous Ethylcellulose Film-Coated Dipyridamole-Loaded Non-Pareil Beads

Marina Levina, Hue Vuong and Ali R. Rajabi-Siahboomi
Colorcon Limited, Flagship House, Victory Way, Crossways, Dartford DA2 6QD, UK

Abstract Summary

This study investigated the influence of hypromellose-based Opadry® pore-former on the release of a poorly water-soluble drug, dipyridamole, from non-pareil beads coated with an aqueous ethylcellulose dispersion (Surelease® NG E-7-19050). It was found that the incorporation of Opadry at various concentrations into the film coating modulated the release of dipyridamole.

Introduction

There is continued 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 distribute more evenly than monolithic dosage forms through the gastro-intestinal tract leading to a reduced risk of local side effects and dose dumping[1]. MP dosage often employ ethylcellulose (EC), a water-insoluble polymer widely used in organic and aqueous film coating applications, to achieve ER drug release.

In this study dipyridamole was used as a poorly water-soluble[2] model drug at 20 mg dose. The objective of this work was to study how the incorporation of water-soluble hypromellose (HPMC), in the form of Opadry and utilized as a pore former in the EC film, influences dipyridamole release from the beads.

Experimental Methods

Dipyridamole (S.I.M.S., Italy) was layered onto a batch of 550-750 µm sugar spheres (NPTAB® 650, NP Pharm S.A.S, France). Opadry OY-29020 Clear (Colorcon), consisting of HPMC E6 and PEG 400, was used as a binder. The viscosity of Opadry solutions in water (10, 12, 15, 18 and 20% w/w) was measured using a Brookfield rheometer.

Dipyridamole was dispersed in the aqueous Opadry solution (8% w/w) and mixed for 45 minutes using a low-shear propeller blender (IKA Labortechnik, Germany). The prepared suspension was then screened through a 250 µm sieve. Drug was layered onto a 1.2 kg batch of the non-pareils in a Glatt GPCG-1.1 (Glatt GmbH, Germany) fluid-bed fitted with a Würster column and 1-mm Schlick spraying nozzle. The drug layering parameters are listed in Table 1.

Drug-layered pellets (0.6kg) were coated with Surelease E-7-19050 (aqueous EC dispersion with oleic acid as a plasticizer[3], Colorcon) to 2.5, 3.5, 5, 7.5, 10 and 12% weight gain (wg). The coating dispersion was prepared by diluting Surelease to 15% w/w solids with purified water.

Table 1. Drug Layering and ER Film Coating Process Parameters

Process Prameter	Values
Fluidising airflow (m^3/h)	85 - 102
Inlet air temperature (°C)	60 - 65
Exhaust air temperature (°C)	41 - 45
Product temperature (°C)	41 - 43
Atomizing air pressure (bar)	1.5
Spray rate (g/min)	6.5 - 10.5

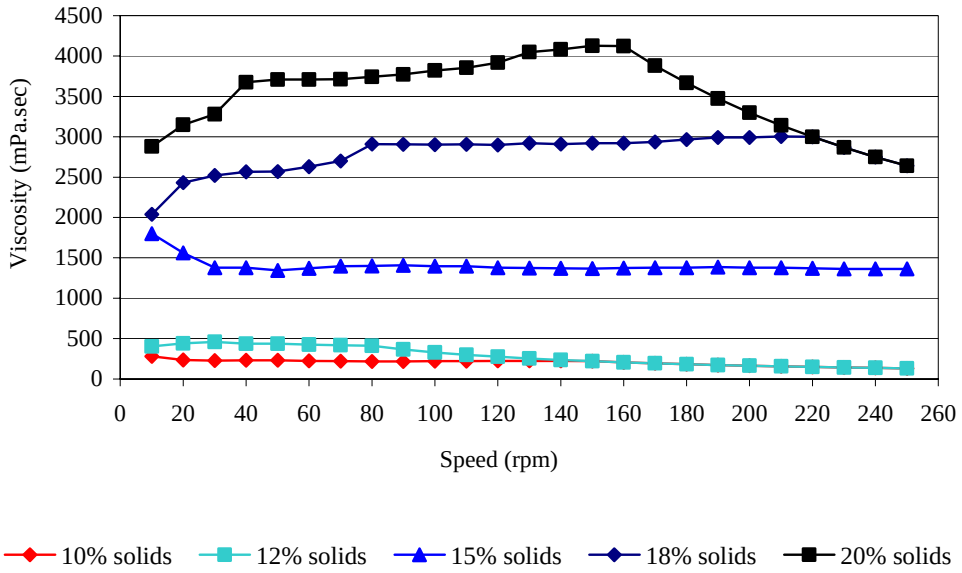
Drug-layered beads were coated with dispersions containing various ratios of Surelease to Opadry OY-29020 to 12% wg in an effort to modulate the release rate of dipyridamole. Opadry was used as a pore-former to adjust the permeability of the EC film, using the coating conditions listed in Table 1.

Drug release was measured from 1 gram of coated beads in a Sotax 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±1°C. A dual beam spectrophotometer (Perkin Elmer) was used for the detection of dipyridamole at a wavelength of 283 nm. The mean of three determinations is reported.

Results and Discussion

For drug layering, various solution concentrations of Opadry OY-29020 were evaluated (Fig. 1). Even though the maximum solids content for spraying was identified as 12% w/w, a concentration of 8% w/w was used in this study due to the dispersions becoming tacky at 10 or 12% w/w.

Fig. 1. Opadry OY-29020 Solution Viscosity Profiles at Various Concentrations in Water



Drug-layered and EC-coated pellets exhibited good appearance, showing no defects in the film coating.

Drug release from the EC-coated pellets was highly reproducible with standard deviations of less than 1% (Fig. 2). The rate of drug release progressively decreased as the coating level increased from 2.5 to 3.5, 5, 7.5, 10 and 12% wg (Table 2). At 12% wg only 50% of the drug was released after 12 hours. Additionally, a lag time developed as the coating level exceeded 5% wg

Fig. 2. Dipyridamole Release from Beads Coated with Aqueous Ethylcellulose without Pore Former

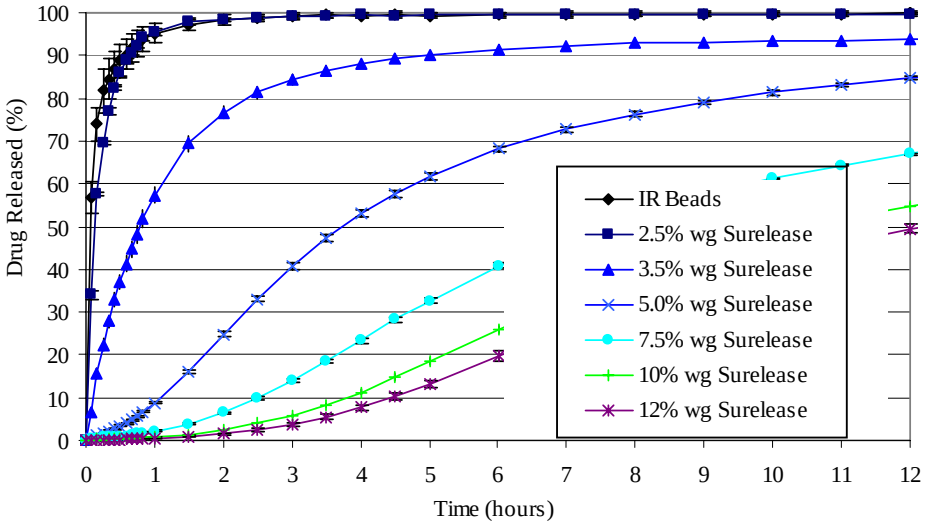


Table 2. The Influence of Surelease Coating Level on Dipyridamole Release (T_{10}%, T_{50}%)

Coating weight gain (%)	T_{10}% (min)	T_{50}% (min)
0.0	1	4
2.5	1	9
3.5	7	47
5.0	65	230
7.5	150	470
10.0	230	650
12.0	267	720

The inclusion of Opadry as a pore-former into the Surelease film increased the dipyridamole release rate (Fig. 3 and Table 3). For samples containing 20% w/w or more pore-former in the EC film, 100% of the drug was dissolved after 12 hours, compared to only 50% released from the film with no pore-former. The enhanced dissolution rate is theoretically due to an increased porosity of the film on coated beads [4, 5]. It has been reported that water-soluble polymers such as HPMC may leach out of the coating, forming a porous film with increased permeability[6] or produce hydrated water filled HPMC regions within the membrane that allow drug transport across the film.

Results also indicated that dipyridamole release rate increased as the Opadry concentration in the coating formulation was increased. This may be due to increased permeability of the film with an increase in the amount of the hydrophilic pore-former used.

It has also been reported[7] that there is a possibility for the occurrence of a critical coating level when using aqueous EC dispersion containing no pore-former. It has been claimed that a mechanically formed porous film, due to incomplete coating, could change to a non-porous film after the pellet has been completely coated. One of the benefits of using pore-former in Surelease is to avoid the possibility of reaching a critical coating level.

Fig. 3. Dipyridamole Release from Beads Coated with Surelease/Opadry to 12% wg

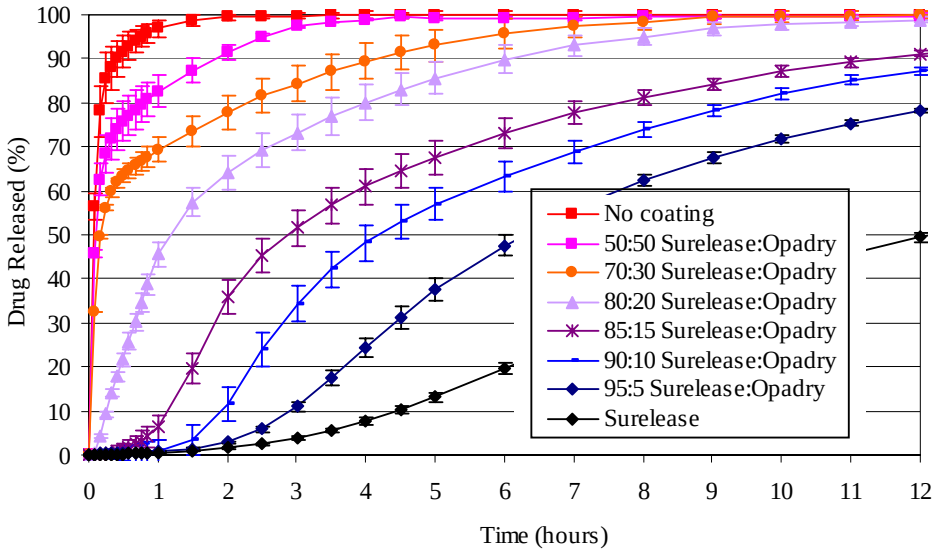


Table 3. The Influence of Opadry Concentration in Surelease Film on Dipyridamole Release from Beads Coated to 12% wg (T_{10}%, T_{50}%)

Opadry concentration (% w/w)	T_{10}% (min)	T_{50}% (min)
Reference (no coating)	1	4
50	1	7
30	2	10
20	16	72
15	68	172
10	115	250
5	175	378
0	267	720

Conclusions

It has been shown that incorporation of Opadry at various concentrations into Surelease E-7-19050 (aqueous ethylcellulose dispersion) film can be used to modulate release of the poorly water-soluble drug dipyridamole.

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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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