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

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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. Ethylcellulose (EC) is a water-insoluble polymer, widely used in organic and aqueous film coating applications to achieve extended drug release.

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 dipyridamole 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>
<thead>
<tr>
<th>Surelease®: Pore Former Ratio</th>
<th>Amount of individual ingredients added (g)</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surelease® dispersion*</td>
<td>Pore former solution**</td>
</tr>
<tr>
<td>95:5</td>
<td>570</td>
<td>50</td>
</tr>
<tr>
<td>90:10</td>
<td>540</td>
<td>100</td>
</tr>
<tr>
<td>85:15</td>
<td>510</td>
<td>150</td>
</tr>
<tr>
<td>80:20</td>
<td>480</td>
<td>200</td>
</tr>
<tr>
<td>70:30</td>
<td>420</td>
<td>300</td>
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</tbody>
</table>

* 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 1](image)

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

![Figure 2](image)
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 f2 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>
<thead>
<tr>
<th>Pore former concentration in Surelease® (% w/w)</th>
<th>( f_2 ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>88</td>
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<tr>
<td>15</td>
<td>59</td>
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<tr>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td>30</td>
<td>99</td>
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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 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.

References

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