Effect of Filler Type on the Stability of Polyethylene Oxide in a Hydrophilic Matrix Tablet

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Abstract
The effect of various fillers on the oxidative stability of polyethylene oxide (PEO) in a matrix tablet was studied. Tablet hardness, dissolution profile, and polymer viscosity were determined to indicate PEO stability can be affected by the type of filler used in the formulation.

Introduction
Polyethylene oxide (PEO) is a water-soluble, nonionic polymer used in controlled-release drug delivery systems. The primary purpose of this study was to address the effect of various fillers on the oxidative stability of PEO in a matrix tablet formulation. Formulation factors were studied, including tablet hardness, drug release, and polymer stability, to evaluate the effect of filler type on the stability of PEO in a hydrophilic matrix tablet. Fillers such as mannitol, lactose, dibasic calcium phosphate, and pregelatinized starch were evaluated in comparison to lactose.

Experimental
Materials
Formulations contained 44.5% filler, 40% POLYOX W301, 5% PEO, and 5% magnesium stearate. Fillers included lactose, mannitol, dibasic calcium phosphate, and pregelatinized starch.

Methods
Formulations were mixed in a v-blender for 10 minutes and directly compressed into 450-mg tablets on a Manesty Beta press at 4000 lb compression force. Tablets were dissolved in deionized water in a USP 2 Apparatus (a Varian Total Solution w/Diss. 230 dissolution system or a Sieve Dissolution System), with a 5-s temperature of 37°C and a paddle speed of 50 rpm. PEO stability was measured by evaluating solution viscosity of dissolved tablets in a 1C-Ubbelohde tube at 37°C. Tablets were weighed using a mortar and pestle and added to 100 ml of distilled water and shaken for 4 hours to dissolve. Each sample was measured in triplicate.

RESULTS AND DISCUSSION
Although several formulation factors (e.g., polymer concentration, polymer molecular weight, drug loading, drug solubility, etc.) have been studied in great detail, direct comparison of the effects of filler have been mainly limited to studies of compaction and compressibility of PEO, lactose, and thalactose (1). Thus, a comparison of the effect of filler type on tablet properties, drug release, and stability was studied.

Tablet Hardness
Table hardness varied with the type of filler in tablet formulations containing PEO (Figure 1). The figure also shows that tablet hardness remained relatively unchanged in all tablet formulations after 3 months storage in the high temperature and high humidity environment.

Drug Dissolution
Figure 2 shows that the performance of PEO in controlling drug release can be moderated by the type of filler used in a matrix tablet formulation. Highly soluble fillers such as lactose and mannitol provided a slower rate of drug release, while poorly soluble fillers such as MCC and DCP provided a faster rate of drug release. MCC and DCP may increase the rate of drug release, providing the slower rate of drug release of all the fillers evaluated. Similar results have been observed in controlled-release matrix formulations containing lactose and starch.

Table 1. Comparison of similarity (Y2) of dissolution profile for PEO formulations to time 0 control

<table>
<thead>
<tr>
<th>Filler</th>
<th>Time (h)</th>
<th>Y2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEO</td>
<td>8</td>
<td>91.4</td>
</tr>
<tr>
<td>PEO</td>
<td>24</td>
<td>91.4</td>
</tr>
<tr>
<td>PEO</td>
<td>72</td>
<td>91.4</td>
</tr>
</tbody>
</table>

Formulations containing lactose and mannitol showed the greatest change in drug release profiles after 1 month of accelerated aging, although exceptions indicate unacceptable similarity (Y2) in drug release from the lactose formulation and near dissimilarity in the mannitol formulation. A comparison of dissolution profile at 5% and 10% for all fillers indicates that MCC, DCP, and Starch 1500 showed minimal similarity over all 3 months.

Viscosity Stability
Viscosity was measured by the relative change in efflux time through the Ubbelohde tube, for the five tablet formulations at 1, 2, and 3 months under accelerated aging conditions and compared to time zero (t = 0) controls. The change in PEO viscosity, as noted by normalized values of time and relative percentage of degradation, is shown in Table 2.

Table 2. Comparison of Ubbelohde measurements (seconds) and viscosity loss (%) for all PEO formulations over time

<table>
<thead>
<tr>
<th>Filler</th>
<th>Time (months)</th>
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<tbody>
<tr>
<td>PEO</td>
<td>0</td>
</tr>
<tr>
<td>PEO</td>
<td>1</td>
</tr>
<tr>
<td>PEO</td>
<td>2</td>
</tr>
<tr>
<td>PEO</td>
<td>3</td>
</tr>
</tbody>
</table>

The changes in viscosity observed here are likely due to the molecular weight of PEO polymer present in the formulation (5). The extent of degradation for PEO formulations was shown to be directly proportional to the viscosity loss. Formulations containing Starch 1500 showed the greatest change in viscosity after 3 months, followed by MCC, lactose, DCP, and mannitol. The Starch 1500 formulation showed virtually no change in viscosity after the first 2 months.

CONCLUSION
PEO stability and consistent drug release were observed to vary with the type of filler used in the matrix tablet formulation. Formulations containing MCC and Starch 1500 showed less than 10% PEO degradation, which relates to the faster rates of drug release observed for the lactose and mannitol formulations. These results indicate that the molecular weight of PEO polymer present in the formulation is directly proportional to the viscosity loss.

REFERENCES