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 profiles, and polymer viscosity were studied over 3 months at accelerated aging conditions. Results 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 solid dosage forms. The primary purpose of this study was to address compatibility concerns between PEO and lactose. Therefore, a study was conducted to evaluate the effect of filler type on the stability of PEO in a hydrophilic matrix tablet. Fillers such as mannitol, dibasic calcium phosphate, microcrystalline cellulose, and pregelatinized starch were evaluated in comparison to lactose. Theophylline, a moderately soluble drug, was used in the formulations. The influence of filler type on tablet hardness, drug release, and PEO stability under accelerated aging conditions is described, and a mechanism relating the impact of filler type to PEO degradation is discussed.

Experimental
Materials
Formulations contained 44.5% filler, 40% POLYOX™ 301 polyethylene oxide, 15% theophylline, and 0.5% magnesium stearate. Fillers included lactose, mannitol, dibasic calcium phosphate (DCP), microcrystalline cellulose (MCC), and pregelatinized starch (Starch 1500, Colorcon).

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 placed in sealed, plastic containers and stored in a humidity-controlled oven at 40°C and 75% relative humidity over a 3-month period. Tablets were evaluated for their physical properties using standard techniques.

The controlled release of theophylline was measured using six tablets from each formulation. The tablets were dissolved in deionized water in a USP 2 Apparatus (a Varian Total Solution w/Dual VK 7025 dissolution system or a Distek Dissolution System), with a bath temperature of 37°C and paddle speed of 50 rpm. PEO stability was evaluated by measuring solution viscosity of dissolved tablets in a 1C Ubbelohde tube at 30°C. Tablets (n = 2 or 3) were individually pulverized using a mortar and pestle and added to 100 g deionized water and shaken for 4 hours to dissolve. Each solution 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 theophylline (1). Thus, a comparison of the relative influence of various fillers in a PEO formulation on tablet properties, drug release, and stability was studied.

Tablet Hardness
Tablet 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 the fastest rate of drug release, while poorly soluble fillers such as DCP and MCC provided a slower rate of drug release. Starch 1500, although slightly soluble to soluble in water, provided the slowest rate of drug release of all the fillers evaluated. Similar results have been observed in controlled-release matrix formulations containing hypromellose (HPMC) (2). Slower drug release from matrices containing PEO and Starch 1500 may be due to the slower penetration of the water front to the matrix core.

Drug dissolution for each of the five tablet formulations was measured at 1, 2, and 3 months under accelerated aging conditions and compared to time zero (t = 0) controls. Examples are shown in Figures 3 through 5. Data for mannitol and MCC are not shown.

Figure 1. Hardness of tablets containing various fillers measured at 0 and 3 months.

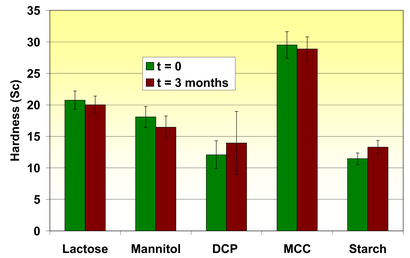


Figure 2. Theophylline dissolution as a function of filler type.

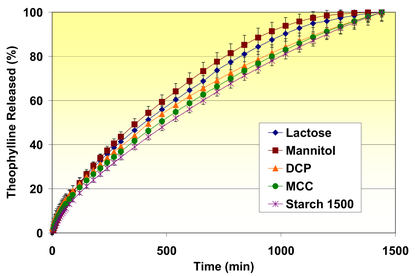


Figure 3. Theophylline dissolution over 3 months (filler: lactose).

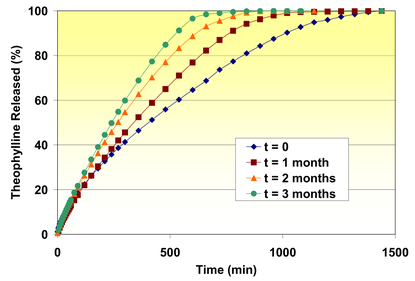


Figure 4. Theophylline dissolution over 3 months (filler: DCP).

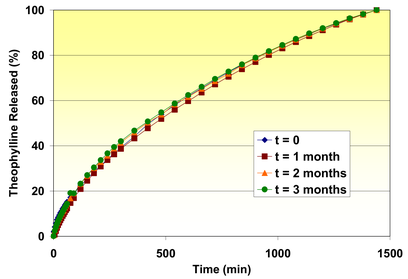
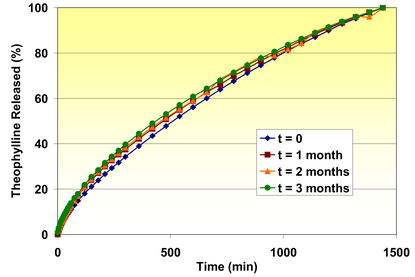


Figure 5. Theophylline dissolution over 3 months (filler: Starch 1500).



Dissolution profile comparisons of normalized drug release as a function of aging are shown in Table 1.

Table 1. Comparison of similarity (f2) of dissolution profiles for PEO formulations to time zero controls.

Filler	Time (months)		
	1	2	3
Lactose	58	46	39
Mannitol	65	54	53
DCP	86	88	88
MCC	92	93	88
Starch 1500	78	74	71

Formulations containing lactose and mannitol showed the greatest change in drug release profiles after 1 month of accelerated aging, although f2 values indicate acceptable similarity between the dissolution profiles in all formulations (3,4). After 2 months, comparison of dissolution profiles to t = 0 profiles indicates unacceptable similarity (f2) in drug release from the lactose formulation and near dissimilarity in the mannitol formulation. A comparison of dissolution profiles at 3 months to t = 0 profiles shows similar results. However, formulations containing DCP, MCC, and Starch 1500 maintained acceptable similarity over all 3 months.

Viscosity Stability
Viscosity loss, as measured by the relative change in efflux time through the Ubbelohde tube, was measured 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.

Filler	t = 0	t = 1 mo	t = 2 mo	t = 3 mo
Lactose				
Efflux time	80±2.2	48±3.3	39±0.2	33±1.7
Visc. loss	—	41%	52%	59%
Mannitol				
Efflux time	82±3.0	54±1.4	52±0.7	47±6.6
Visc. loss	—	35%	38%	43%
DCP				
Efflux time	129±7.5	122±5.4	126±0	128±8.5
Visc. loss	—	6%	3%	1%
MCC				
Efflux time	129±3.3	119±6.4	117±3.5	118±7.8
Visc. loss	—	8%	10%	9%
Starch 1500				
Efflux time	118±6.1	127±19.8	125±9.2	115±1.7
Visc. loss	—	-8%	-6%	3%

The changes in viscosity observed here are likely due to changes in the molecular weight of PEO polymer present in the formulation (5). Degradation of PEO is shown to be more prevalent in the lactose and mannitol formulations. The results indicate a consistent loss of viscosity for the lactose formulation over the 3 months. The mannitol formulation showed a similar viscosity loss after 1 month, but the rate of viscosity loss appears to slow down thereafter. For formulations containing DCP, MCC, or Starch 1500, viscosity loss was less than 10% after 3 months. The Starch 1500 formulation showed virtually no change in viscosity after the first 2 months.

The changes in drug release observed in the dissolution profiles correlate to changes observed in viscosity for each formulation. It is reasonable to assume that the faster rates of drug release observed for the lactose and mannitol formulations are due to degradation of PEO molecular weight. Further, the similarity of dissolution profiles for DCP, MCC, and Starch 1500 formulations maintained over 3 months compares accordingly to viscosity results which indicate minimal viscosity loss.

The degradative effect of lactose, a reducing sugar, and of mannitol, a reducible organic compound, on PEO may be due to their relative ease of aerobic autooxidation, resulting in the generation of active oxygen species and causing heterolytic depolymerization of high molecular weight PEO. While the extent of depolymerization is probably low, small changes in PEO molecular weight exhibit significant impact on solution viscosity and on the ability of PEO to control the rate of drug dissolution. Similar polymer degradative effects of reducing sugars and of mannitol have been reported with DNA (6,7), peptides and proteins (8–10), active oxygen-sensitive drugs (10), and polysaccharides (11). Additional work is planned to better define the chemical mechanism of PEO viscosity degradation.

CONCLUSION
PEO stability and concomitant drug release were observed to vary with the type of filler used in formulations containing PEO. PEO degradation was more prevalent in formulations containing lactose and mannitol, which is related to an increase in drug release rates under accelerated aging conditions. Formulations containing DCP, MCC, and Starch 1500 showed less than 10% PEO degradation, which relates to minimal viscosity loss. These results indicate that the molecular weight stability of PEO in a matrix tablet can be affected by the type of filler used in the formulation, which ultimately may alter drug release profiles.

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