

The Use of Polyethylene Oxide Mixtures to Study Formulation Robustness in Hydrophilic Extended Release Matrix Tablets

Jennifer L'Hote-Gaston,[†] Robert Schmitt,[†] Marina Levina,[‡] Guang Wen,[‡] Ali Rajabi-Siahboomi[†]

[†]The Dow Chemical Company, Midland, MI 48642, and Bound Brook, NJ 08854 USA

[‡]Colorcon, Inc., West Point, PA 19486 USA

Objective

Demonstrate the use of polyethylene oxide blends to investigate the effect of polymer viscosity on formulation robustness.

Introduction

Robustness in pharmaceutical solid oral dosage forms means consistently providing the same drug dissolution performance and shelf life from the dosage form when manufactured within the limits of the defined variations of key quality parameters. These parameters include excipients, active pharmaceutical ingredients (API), and the manufacturing process. Under ideal circumstances, formulators would have raw materials available to them with a broad range of properties with which to conduct studies to assess the impact of excipient variability on formulation robustness. Realistically, however, the ability of the supplier to manufacture materials at the extremes of specification is challenging given that manufacturing processes are designed to operate under optimal conditions to produce a consistent product.

For polyethylene oxide (PEO), blends may be the answer. When formulating extended release (ER) matrix systems, the key PEO attributes that affect drug dissolution are polymer viscosity and particle size distribution. Because PEO does not have the additional complication of chemical substitution seen with many other excipients, blending is a straightforward approach that can be used to produce samples for formulation studies provided the performance of the polymer blend is representative of the standard product. PEO blends can provide a range of samples across a specification to achieve the necessary variability in viscosity more easily than using batches of a single PEO product. These samples can then be used to assess the impact of material viscosity variability on formulation properties. This study used two standard PEO polymers (POLYOX™ 205 NF Water Soluble Resin and POLYOX™ N-12K NF Water Soluble Resin) to develop a series of samples across the viscosity specification range of another standard product (POLYOX™ 1105 NF Water Soluble Resin), which has a viscosity between these two grades. Polymer viscosity, molecular weight, tablet mechanical strength, and drug dissolution were determined to evaluate the effect of PEO blends on excipient performance in hydrophilic extended-release matrix tablets.

Materials and Methods

Materials

PEO polymers used for blending included POLYOX 205 and POLYOX N-12K (The Dow Chemical Company, Midland, MI USA) with approximate molecular weights of 6x10⁶ and 1x10⁶ Daltons, respectively. Excipients used as standards for comparison were three samples of POLYOX 1105 (The Dow Chemical Company, Midland, MI USA), varying in solution viscosity and with an approximate molecular weight of 9x10⁶ Daltons. Theophylline and diltiazem hydrochloride (Spectrum, Gardena, CA USA) were used as model APIs. Other ingredients included microcrystalline cellulose (Avicel PH 102, FMC Biopolymer, Newark, DE USA), and magnesium stearate (Spectrum, Gardena, CA USA).

Methods

Three blends (25/75, 50/50, and 75/25) were prepared with POLYOX 205 and POLYOX N-12K using a Turbula mixer (Willy A. Bachofen AG, Muttenz, Switzerland). Viscosity determinations for PEO samples were made using a Brookfield DV-II+ viscosimeter (Brookfield Engineering, Middleboro, MA USA), 5% aqueous solution, with spindle 2 at 2 rpm, except for the sample of POLYOX N-12K, which was run at 2% aqueous solution, spindle 1 at 10 rpm.

Weight-average molecular weight (M_w), number-average molecular weight (M_n), and polydispersity, (PDI) were determined by aqueous size exclusion chromatography with a multi-angle laser light scattering detector (SEC-MALLS). The SEC system consisted of a Waters 2690 pump (Waters Corp., Milford, MA USA) connected with a Wyatt DAWN-EELS detector and Wyatt differential refractive index detector (Wyatt Technology Corp., Santa Barbara, CA USA). The SEC fractionation of analyzed sample was evaluated to ensure an ideal SEC separation was obtained.

Extended-release matrix formulations comprised 40% w/w API, 30% w/w polymer or polymer blend, 29.5% w/w MCC, and 0.5% w/w magnesium stearate. Tablets with a target weight of 400 mg were prepared by direct compression using a Manesty Beta 16-station tablet press (Oyster Manesty, Merseyside, England) equipped with 0.4063-inch (10.2-mm) flat-faced, bevel-edge tooling at a compression force of 4000 lb (17.8 kN). Mechanical strength of the matrices (n=10) was measured with a hardness tester (Model HT-300, Key International, Englishtown, NJ USA). Drug dissolution (n=6) was determined in a USP II Apparatus, Vankel VK 7025 dissolution system (Varian Inc., Palo Alto, CA USA) with UV-Vis spectrophotometer, using three-pump capsule weights, in deionized water at 37.0±0.5°C, and a paddle speed of 50 rpm.

References are available upon request.

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 Form No. 198-02205

Table 1. Properties of PEOs, PEO blends, and tablets prepared from theophylline and diltiazem HCl formulations.

Sample	Brookfield Viscosity (cP)		M _w (Daltons)	M _n (Daltons)	PDI	Breaking Force (Theophylline)		Breaking Force (Diltiazem HCl)	
	Ave. Visc.	SD				(esu)	SD	(esu)	SD
POLYOX 1105 (A)	11520	85	1.17x10 ⁶	2.59x10 ⁵	4.52	26.2	0.9	19.4	0.7
POLYOX 1105 (B)	9250	212	1.09x10 ⁶	2.09x10 ⁵	5.21	25.7	1	18.8	0.6
POLYOX 1105 (C)	9120	198	1.05x10 ⁶	1.83x10 ⁵	5.74	25.2	1.6	18.4	0.5
POLYOX 205 NF	6690	120	9.76x10 ⁵	2.50x10 ⁵	3.91	—	—	—	—
POLYOX N-12K	430	7.1	1.32x10 ⁵	2.61x10 ⁴	5.03	—	—	—	—
25/75 POLYOX 205:N-12K (D)	17700	792	1.25x10 ⁶	2.82x10 ⁵	4.46	26.9	1	21.8	0.6
50/50 POLYOX 205:N-12K (E)	12720	1838	1.13x10 ⁶	2.59x10 ⁵	4.35	27.5	1.1	22.1	0.4
75/25 POLYOX 205:N-12K (F)	9630	99	1.04x10 ⁶	2.41x10 ⁵	4.32	27.1	0.9	21.4	0.9

Figure 1. Theophylline release from matrices containing PEO or PEO blends.

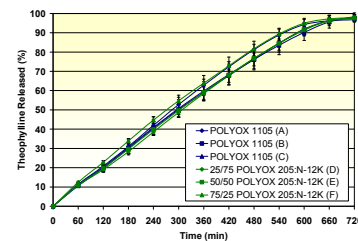


Figure 3. Rate of theophylline release from matrices containing PEO or PEO blends.

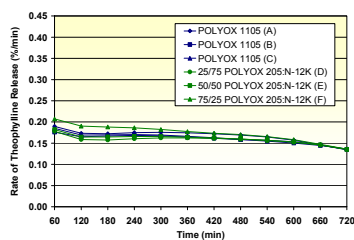


Figure 2. Diltiazem HCl release from matrices containing PEO or PEO blends.

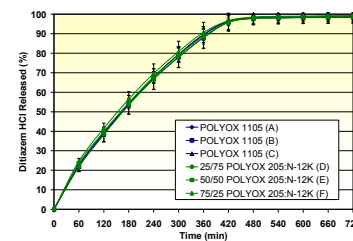
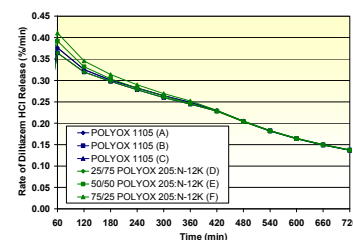


Figure 4. Rate of diltiazem HCl release from matrices containing PEO or PEO blends.



Results and Discussion

Effect of Blending on Polymer Viscosity

Table 1 compares the viscosity values for blended PEO samples to individual samples of POLYOX 205, POLYOX 1105, and POLYOX N-12K. Samples (A, B, and C) of commercially available POLYOX 1105 only covered a narrow viscosity range of 9,120–11,520 cP within the broader product viscosity specification of 8,800–17,600 cP. The lack of POLYOX 1105 samples with viscosities at the upper extreme of the product specification makes it difficult to assess the impact of variability in product viscosity on matrix formulation properties. Thus, blends of POLYOX 205 and POLYOX N-12K (D, E, and F samples) were prepared in varying proportions to achieve a range of viscosities representative of POLYOX 1105 product viscosity. The results showed that blending of PEO products adjacent to the targeted POLYOX grade is a reasonable approach for obtaining representative viscosities for formulation testing.

Effect of Blending on Polymer Molecular Weight

Table 1 shows the molecular weight results obtained via SEC-MALLS for POLYOX 1105 samples, the POLYOX 205 and POLYOX N-12K blend components, and the blends. The M_w values of the blends were between the values for each component, decreasing with increasing amounts of the lower M_w component (POLYOX 205). Standard deviations for the blends were <1.6%. The M_w values for the POLYOX 1105 samples were very similar, with standard deviations of <0.36% that indicated excellent reproducibility of the SEC-MALLS measurement. A comparison of the approximate molecular weight of standard POLYOX WSR samples provided in product literature (viscosity average molecular weight) to the molecular weight determined by SEC-MALLS (weight average molecular weight) shows significantly higher values for the SEC measurement. As discussed by Flory (1), viscosity average molecular weight M_v should be M_w>M_v>M_n for polymers with a PDI>1. This principle explains why molecular weight data in product literature is not directly comparable to the results obtained by SEC-MALLS.

Molecular weight distribution (MWD) obtained via SEC-MALLS showed little difference between POLYOX 1105 individual samples and both the POLYOX 205 and POLYOX N-12K blend components or the blends themselves. PEO showed a broad molecular weight distribution regardless of polymer molecular weight (data not shown). The molecular weight distribution can vary to some degree for a specific PEO product as observed for POLYOX 1105 (A, B, and C) where PDI ranged from 4.52 to 5.74 (Table 1). The molecular weight distributions for POLYOX 205 and POLYOX N-12K blend components were similar to that of POLYOX 1105. Blends of POLYOX 205 and POLYOX N-12K (D, E, and F) also had molecular weight distributions similar to POLYOX 1105 (data not shown). Neither bimodality nor high-end tailing was observed in the blends. The SEC-MALLS results showed that blending of PEO products adjacent to the targeted POLYOX grade does not adversely impact molecular weight distribution.

Effect of Polymer Blending on Tablet Breaking Force

Table 1 shows that tablet breaking force was significantly higher (Anova, P<0.05) for both theophylline and diltiazem HCl matrices containing PEO blends when compared to the formulations where standard POLYOX 1105 product was used. The variation in tablet mechanical strength was relatively small (0.5% for theophylline matrices as opposed to diltiazem HCl matrices (13%) when comparing formulations with PEO blends to the formulations where standard POLYOX 1105 product was used. The variation was thought to be due to particle size effects in the PEO blends that require a further investigation.

Effect of Polymer Blending on Drug Release

A comparison of drug release was made using the similarity factor, f₂ (2, 3). The FDA has set a standard of f₂ value between 50 and 100 to indicate a similarity between two dissolution profiles. Drug release from theophylline (Figure 1) and diltiazem HCl (Figure 2) matrices showed acceptable similarity for all formulations (f₂>75 and f₂>82, respectively). This indicated that the viscosity of PEO, whether as an individual product or a blend, did not significantly affect drug dissolution within the evaluated range.

The rate of drug release for formulations with PEO blends showed more variation in the first several hours of dissolution with the theophylline (Figure 3) than with the diltiazem HCl (Figure 4) formulation, suggesting that viscosity of PEO blends is slightly sensitive to drug solubility.

Conclusions

Blends of PEO polymers varied viscosities across the range of a standard POLYOX product specification and remained consistent with the typical PEO product to which it was compared. Molecular weight and polydispersity for PEO blends were consistent with the standard POLYOX products, which showed a typical unimodal distribution. When comparing drug dissolution profiles from matrix tablets, the PEO blends showed a good f₂ similarity to typical POLYOX products. For theophylline formulations containing PEO blends, the rate of drug release showed more variation in the first several hours of dissolution, suggesting that variability in the viscosity of PEO blends is slightly sensitive to drug solubility. This study demonstrates a reasonable approach to assess the impact of excipient variability in formulation development by blending standard excipient products, and has practical implications in the design of robust extended-release, PEO-based matrix formulations.