

FORMULATING CUSTOM VISCOSITY BLENDS WITH POLYOX™ POLYETHYLENE OXIDE

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ABSTRACT

POLYOX™ PEO (Polyethylene Oxide) water-soluble polymers are renowned for their rapid hydration properties. They are available in a diverse range of molecular weight grades, spanning from 100,000 to 7,000,000 Dalton. POLYOX™ PEO water-soluble resins exhibit exceptional hydrophilicity, leading to swift hydration and the formation of a gel layer on matrix tablet surfaces to facilitate the release of the drug substance. Notably, an increase in molecular weight corresponds to higher polymer viscosity and, consequently, enhanced gel strength. Understanding the impact POLYOX™ PEO viscosity (especially the high and low ends of the viscosity specification range) has on product performance can be an important aspect of quality-by-design (QbD). One of the key QbD challenges in using POLYOX™ PEO is acquiring batches of a given viscosity grade that are at the viscosity specification extremes. The present study showcases the advantage of blending of two different POLYOX™ PEO grades in varying ratios to attain the desired lower and upper viscosity specification limits. This approach empowers scientists to explore the effects of different viscosities on drug release formulations. By blending different POLYOX™ PEO grades in specific proportions, we can precisely tailor the gel strength, providing valuable insights for robust drug delivery.

INTRODUCTION

Quality-by-design (QbD) is the concept that quality should be built into the design of a pharmaceutical product, not tested into a product. [1] A robust drug product will withstand natural and expected

manufacturing and raw material variability to consistently deliver the intended product performance to the patient. To ensure the robustness of a finished dosage form, it is crucial to thoroughly test the formulation's key attributes that influence drug release. This approach not only aids in achieving consistency in drug dissolution but also contributes to the development of safe and effective dosage forms. Additionally, investigating the key attributes of functional polymers, particularly those that may impact drug product performance, plays a pivotal role in guaranteeing the quality of the final product.

Excipient variability should be taken into consideration in a risk-based and scientific approach to QbD. While many excipient manufacturing processes are designed to produce material with targeted properties, some variability is inevitable, subsequently giving rise to specification ranges. One such example is POLYOX™ PEO (Polyethylene Oxide), a homopolymer with controlled molecular weight, and consequently, viscosity. Although the manufacture process may target a viscosity value for a given grade, some batch-to-batch variability within the product specification range exists. Because this batch-to-batch variability may impact drug product performance, it therefore should be assessed on a case-by-case basis for a given drug product. The main material attribute of PEO is its polymer viscosity, which may significantly affect drug dissolution. A previous study has shown the most important factor in predicting drug dissolution from a POLYOX™ PEO based matrix is the PEO viscosity, whether it is from a single batch or a blend of different grades of POLYOX™ PEO. [2]

The common QbD approach to assessing the impact of polymer viscosity on drug product performance is to evaluate the extreme values of a product specification range. This is not always possible given the manufacturing challenges associated with producing polymer material at the specification extremes (manufacturing process are not typically designed to make extremes). To address manufacturing challenges, one effective strategy is to blend different grades of POLYOX™ PEO to achieve a range of viscosities within the polymer specifications. These blended samples can then be used to assess the impact of viscosity on the dissolution of drug formulations.

In this study, we employed different molecular weight (MW) grades of POLYOX™ Polyethylene Oxide polymers (~1,000,000 to 7,000,000 Da in MW)) in various ratios to create blends, and subsequently compared the theoretically calculated viscosities with the actual test results. This comprehensive analysis provides a tool with which formulators can use to estimate blend ratios of two different grades of PEO based on their starting viscosity. Ultimately, these blends can be tested within a formulation to determine robustness to viscosity changes within a product's viscosity specification range.

METHODS

Materials

POLYOX™ WSR N12K LEO NF (~1,000,000 Dalton), POLYOX™ WSR N60K LEO NF (~2,000,000 Dalton), POLYOX™ WSR 301 LEO NF (~4,000,000 Dalton), POLYOX™ WSR Coagulant LEO NF (~5,000,000 Dalton), POLYOX™ WSR 303 LEO NF (~7,000,000 Dalton) were obtained from the IFF sample center and used as received. For simplicity, the WSR (water soluble resin), LEO (low ethylene oxide) and NF (National Formulary) designations for each grade may be dropped from the POLYOX™ PEO name in the subsequent sections. Isopropanol, anhydrous, 99% purity, was obtained from Fisher Scientific. Deionized water (DI) was obtained via Milli-Q EQ 7000 model from Merck Life Science Private Limited.

Viscosity testing

Viscosity of each grade was tested as per the IFF viscosity method PSM 101962-E19F based upon the USP43 NF 38 monograph. IFF uses Brookfield RV Series Viscometer available from Brookfield Engineering Laboratories, Inc. and Brookfield RV Series spindle set, with spindle guard, available from Brookfield Engineering Laboratories, Inc. Isopropanol was used to initially disperse the PEO powder prior to hydration to prevent gel clumps. Please refer to current monograph or request for IFF method of analysis for further details. A summary of method is described below.

Pass a 50-gram sample of PEO through a 20-mesh screen and weigh the required quantity of sample into 800 mL beaker based on the solution concentration to be prepared as indicated on the specification. Weigh DI water into another beaker based on the solution concentration to be prepared. Add 125 mL of Anhydrous Isopropanol into the beaker containing the sample and stir the solution at 300-400 rpm to ensure slurry is formed (must use multi-paddle stirring rod as outlined in the method). While stirring, pour, but do not dump, the pre-weighed water into the isopropanol slurry and allow to stir for one minute at 300-400 rpm. Reduce the speed of the stirrer to 60 rpm, ensuring the top paddle is just skimming the top of the solution, and cover the beaker around the shaft and stir for around three hour ± 15 minutes. After completion of stirring, confirm no gel lumps are present and place the sample beaker in circulating water bath set at 25°C; cover with watch glass for minimum 30 minutes or till the solution reaches temperature of 25±0.1°C across the beaker (typical equilibration time is two hour – three hours) by verifying with the thermometer. Once the target temperature of the sample solution is reached, measure the viscosity of the solution using RV model Brookfield viscometer; details such as % concentration, spindle, speed (rpm) and read time are provided in Table 1 (per the IFF method). Viscosity measurements were taken once per sample.

POLYOX™ WSR Product	% Solution	Spindle	Speed, rpm	Read Time, min
N12K	2	1	10	1
N60K	2	3	10	1
301	1	2	2	5
Coagulant (COAG)	1	2	2	5
303	1	2	2	5

Table 1. POLYOX™ PEO grades and respective spindle, speed and read time for viscosity testing

BLENDING OF SOLID POLYMER AND VISCOSITY TESTING

POLYOX™ N60K was taken as mid-viscosity polymer and blended with POLYOX™ N12K (to target the lower viscosity range) and POLYOX™ 301 (to target the upper viscosity range). Additional blends of N12K and N60K were created to build out the blend ratio vs viscosity model. POLYOX™ Coagulant (abbreviated as COAG) was chosen as a high-viscosity grade with which to blend in POLYOX™ 301 (to target the lower viscosity range) and POLYOX™ 303 (to target the upper viscosity range). First, individual solutions of the grades were made per their specified solids content in Table 1 to obtain the true starting viscosity of each grade. For the grade blends, solid polymers were blended at different ratios in an octa blender for five mins as per Table 2. After blending, the solutions of the blends were prepared as described in viscosity testing method above. The spindle, speed and read times (noted in the results tables) were determined such that the torque readings of the Brookfield Viscometer were between 10 and 90%.

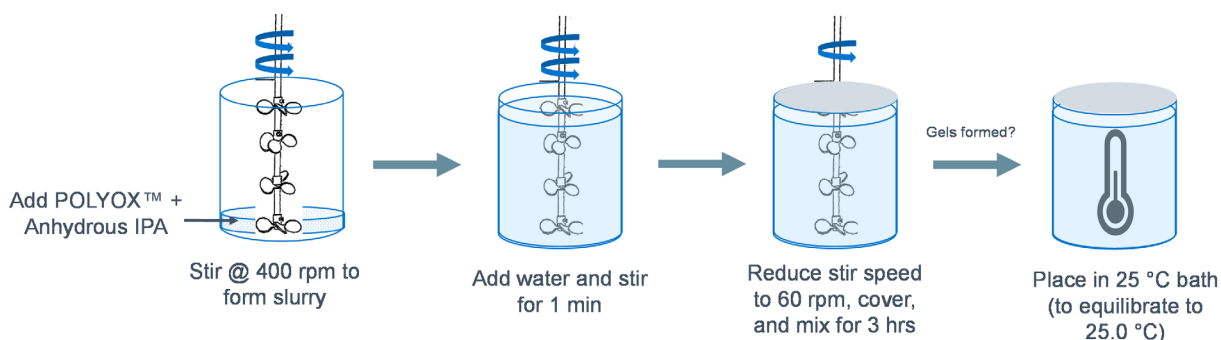


Figure 1. Diagram of how to make POLYOX™ PEO solutions.

BLEND RATIOS (%)							
POLYOX™ WSR N60K LEO NF (2 wt% solution)	10	20	40	50	60	80	90
POLYOX™ WSR N12K LEO NF (2 wt% solution)	90	80	60	50	40	20	10
BLEND RATIOS (%)							
POLYOX™ WSR N60K LEO NF (2 wt% solution)	10	20	40	50	60	80	90
POLYOX™ WSR 301 LEO NF (2 wt% solution)	90	80	60	50	40	20	10
POLYOX™ WSR COAG LEO NF (1 wt% solution)	15	20	25	-	-	-	-
POLYOX™ WSR 303 LEO NF (1 wt% solution)	85	80	75	-	-	-	-
BLEND RATIOS (%)							
POLYOX™ WSR COAG LEO NF (1 wt% solution)	90	-	-	-	-	-	-
POLYOX™ WSR 301 LEO NF (1 wt% solution)	10	-	-	-	-	-	-

Table 2. List of POLYOX™ PEO blend ratios

The spindle, speed and read time were chosen for the blended solutions such that the torque of the Brookfield remained stable and between 10-90%. When the torque is less than 10% or above 90%, viscosity readings become less accurate.

PREDICTIVE VISCOSITY MODELS

The method uses weight fraction of two polymer and actual viscosities to theoretically predict the viscosity of the blend. Five different blending models were used, and the calculations were compared to the actual results to determine if any one model best predicts POLYOX™ PEO blend viscosities. For all models η_{12} is the estimated viscosity of the blend of components one and two, η_1 is the viscosity of component one, η_2 is the viscosity of component two, x_1 is the weight fraction of component one, and x_2 is the weight fraction of component two.

Model 1

The first model is known as the Arrhenius equation and is expressed below. [3]

$$\ln(\eta_{12}) = x_1 * \ln(\eta_1) + x_2 * \ln(\eta_2) \quad (\text{Equation 1})$$

The results are shown as Model 1 Viscosity in the tables below.

Model 2

The second model is the METHOCEL™ HPMC blend predictive model as outlined in the METHOCEL™ Technical Handbook. [4]

$$\eta_{12}^{\left(\frac{1}{8}\right)} = x_1 * \eta_1^{\left(\frac{1}{8}\right)} + x_2 * \eta_2^{\left(\frac{1}{8}\right)} \quad (\text{Equation 2})$$

The results are shown as Model 2 Viscosity in the tables below.

Model 3

The third model is known as the Refutas model and consists of several parts. [3] The individual components each have a viscosity blending index, A_i :

$$A_i = 14.534 * \ln[\ln(\eta_i + 0.8)] + 10.975 \quad (\text{Equation 3})$$

The average blend viscosity index is A_{12} :

$$A_{12} = x_1 * A_1 + x_2 * A_2 \quad (\text{Equation 4})$$

The blend viscosity is calculated using the average blend viscosity index:

$$\eta_{12} = \exp \left[\exp \left(\frac{A_{12} - 10.975}{14.534} \right) \right] \quad (\text{Equation 5})$$

The results are shown as Model 3 Viscosity in the tables below.

Model 4

The fourth model is the Kendall & Monroe model that estimates the blend viscosity from the cubic-root average of the components. [3]

$$\eta_{12}^{1/3} = x_1 * \eta_1^{1/3} + x_2 * \eta_2^{1/3} \quad (\text{Equation 6})$$

The results are shown as Model 4 Viscosity in the tables below.

Model 5

The fifth model is the Bingham model that correlates the inverse of the viscosities (fluidity) of the components with the blend viscosity. [5]

$$\frac{1}{\eta_{12}} = \frac{x_1}{\eta_1} + \frac{x_2}{\eta_2} \quad (\text{Equation 7})$$

The results are shown as Model 5 Viscosity in the tables below.

RESULTS

Prior to blending different grades of POLYOX™ PEO, the individual grade viscosities were determined in-house (rather than using the viscosity listed on the certificate of analysis [COA]). As Polyethylene Oxide (PEO) polymers are known for auto-oxidative degradation impacting viscosity and stability, actual viscosity at the time of experiment was taken for predictive viscosity calculation. Table 3 shows comparison of measured viscosity against the reported COA value.

Material Name	Batch No.	COA viscosity, mPa.s	Measured viscosity, mPa.s	Product specification, mPa.s
SENTRY POLYOX™ WSR N12K LEO ^a NF	D682H5APL6	584	520	400-800 (2% solution)
SENTRY POLYOX™ WSR N60K LEO NF	D682I3TPM3	2880	2700	2000-4000 (2% solution)
SENTRY POLYOX™ WSR 301 LEO NF	D682IAOPB3/ D682H8PPB4 ^b	3760/ 3220	3760/ 3360	1650-5500 (1% solution)
SENTRY POLYOX™ WSR COAG LEO NF	2744196523/ 2744151987 ^c	5980/ 6913	5060/ 6140	5500-7500 (1% solution)
SENTRY POLYOX™ WSR 303 LEO NF	D682IAOPB3	8590	7780	7500-10,000 (1% solution)

Table 3. Measured viscosity of POLYOX™ solutions per conditions in Table 1 against the COA value
^aLEO - Low ethylene oxide. The only difference between these grades and the standard grades (non-LEO) is the residual ethylene oxide specification: less than or equal to one ppm for LEO and less than or equal to 10 ppm for standard grades.
^bTwo different lots of POLYOX™ 301 were used in the studies below. The first batch listed was used to develop the blends of POLYOX™ N60K and 301. The second batch was used in the blends of POLYOX™ Coagulant and 301.
^cTwo different lots of POLYOX™ Coagulant were used in the studies below. The first batch listed was used to develop the blends of POLYOX™ Coagulant and 303. The second batch was used in the blends of POLYOX™ Coagulant and 301.



BLEND OF POLYOX™ N60K WITH POLYOX™ N12K

The first case study targeted the extremes of the viscosity specification range of POLYOX™ N60K by blending N60K with a lower viscosity grade (N12K) and a higher viscosity grade (301) at different ratios. Blending and estimating the blend viscosity of POLYOX™ N60K and POLYOX™ N12K grades is straightforward since both COA viscosities are measured on two wt% solutions. The blends were prepared per Table 2 and the viscosities were measured using Spindle #3 at 10 rpm read after one min. The torque values of the Brookfield Viscometer fell between 27 and 70% of the max, which is well within the suggested range of 10 and 90%. The theoretically predicted viscosity was calculated using each blend model and compared with the observed blend viscosity. The percentage difference between predicted and measured value was noted.

Results show that the predictive viscosity models all under-predict the actual blend viscosity (Table 4 and Figure 1). In general, the models all have higher predictive power when one of the components of

the blend is at or above 80%. This result is positive for use of the models targeting the viscosity specification extremes since most cases would call for a minimal addition of the secondary grade to the main grade of interest. The highest deviations per model (ranging from -11 to -40%) were typically observed at 50/50 or 60/40 ratios (Table 5). Most models had less than 20% deviation from the measured viscosity, with one model (Model 4: Kendall & Monroe) typically having less than 10% deviation, thereby best predicting the blend viscosity across the entire range. For this case, Model 5 (Bingham) showed the most deviation from the actual viscosity values and would not be the optimal choice when blending these two POLYOX™ PEO grades.

The blend of POLYOX™ N60K and POLYOX™ N12K is meant to target the lower viscosity specification of N60K (2,000 mPa.s) or the upper viscosity specification of N12K (800 mPa.s). Models one through four correctly estimate a blend of approximately 80% N60K and 20% N12K (with these starting viscosities), resulting in a blend viscosity of approximately 2,000 mPa.s. These same four models also most accurately predict the blend ratio needed to hit the upper viscosity spec of N12K (800 mPa.s) using these two batches: 80% N12K and 20% N60K.

POLYOX™ WSR N60K LEO NF	POLYOX™ WSR N12K LEO NF	Model 1 Viscosity, mPa.s	Model 2 Viscosity, mPa.s	Model 3 Viscosity, mPa.s	Model 4 Viscosity, mPa.s	Model 5 Viscosity, mPa.s	Actual Viscosity, mPa.s
0	100*	N/A	N/A	N/A	N/A	N/A	520
10	90	613	623	603	643	566	680
20	80	723	744	702	783	620	880
40	60	1005	1047	960	1123	768	1230
50	50	1185	1236	1130	1325	872	1420
60	40	1397	1454	1334	1549	1009	1670
80	20	1942	1993	1882	2072	1469	2160
90	10	2290	2323	2250	2372	1902	2380
100	0	N/A	N/A	N/A	N/A	N/A	2700

Table 4. POLYOX™ N60 with POLYOX™ N12K at 2% solution Spindle 3, rpm 10, min 1

*Spindle 1 and 10 rpm per method for N12K

% Deviation from Actual Viscosity						
POLYOX™ WSR N60K LEO NF	POLYOX™ WSR N12K LEO NF	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
0	100	N/A	N/A	N/A	N/A	N/A
10	90	-10	-8	-11	-5	-17
20	80	-18	-15	-20	-11	-30
40	60	-18	-15	-22	-9	-38
50	50	-17	-13	-20	-7	-39
60	40	-16	-13	-20	-7	-40
80	20	-10	-8	-13	-4	-32
90	10	-4	-2	-5	-0.3	-20
100	0	N/A	N/A	N/A	N/A	N/A

Table 5. Percent deviation of model predictions from actual blend viscosity

POLYOX™ N60K and N12K Blends (2wt% solutions)

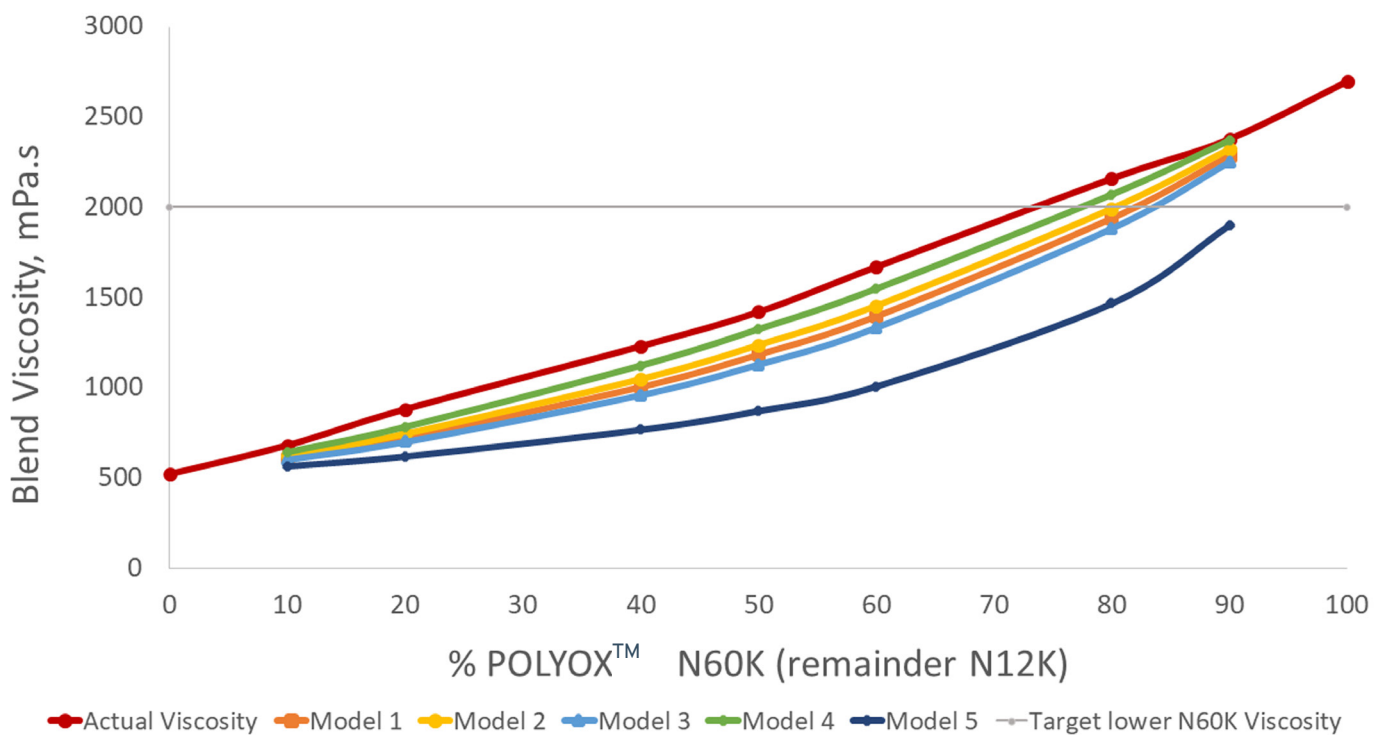


Figure 2. Predicted (Models 1-5) and actual (red curve) viscosities of POLYOX™ N60K and N12K batches.



BLEND OF POLYOX™ N60K WITH POLYOX™ 301

To target the upper viscosity specification of POLYOX™ N60K (4000 mPa.s), we need to add a fraction of the next highest molecular weight grade: POLYOX™ 301. The challenge with blending these two grades is that the viscosity specification (and thus reported COA viscosity) is measured on a two wt% basis for N60K, but on a one wt% basis for 301. When estimating the blend viscosity of these two grades to hit the upper viscosity specification of N60K, we must estimate a two wt% solution of 301 (making this directly is very challenging and adds an extra step to the estimation process). The Polyethers chapter of Kirk-Othmer [6] contains a viscosity-versus-concentration plot of different molecular weight PEO. Using this plot, we can estimate the relationship between solution concentration, c_{301} , and viscosity, η_{301} to be approximately (exponential fit of data estimated from the graph):

$$\eta_{301} = 3108.9 \times c_{301}^{2.8683}$$

The extrapolated two wt% solution viscosity is 20,745 mPa.s. In practice, some deviation is expected from this value and the actual two wt% viscosity of any given batch of 301, since all batches will have slight variation in molecular weight distributions and thus solution viscosities. The Kirk-Othmer example has a one wt% solution viscosity of approximately 3000 mPa.s, which is close to our batch that has a 1% solution viscosity of 3760 mPa.s. We can adjust for this difference by estimating a linear relationship between the two batches (one and two):

$$\frac{\eta_{1\%,1}}{\eta_{2\%,1}} = \frac{\eta_{1\%,2}}{\eta_{2\%,2}}$$

Our batch with 1% solution viscosity of 3760 mPa.s may have a 2% solution viscosity of 26,000 mPa.s. This value is used in the model calculations to estimate the blend viscosities of N60K and 301 at two wt% solutions. The challenge with estimating the two wt% viscosity of the POLYOX™ 301 batch is that the predictive powers of the blend models are now dependent on the predictive power of the concentration model. The more accurate we predict the two wt% viscosity of POLYOX™ 301, the better the blend viscosity models will estimate the true blend viscosity.

Once again, we see the models are most predictive of the blend viscosity when the second component concentration is minimized (less than 20 wt%, Table 6 and Figure 2). As the blend ratio reaches 50/50, the models significantly deviate from the actual blend viscosity (Table 7), with errors as great as 57% (Model 4: Kendall & Monroe) and as low as 21% (Model 3: Refutas). It is interesting to note that the best blend model for POLYOX™ N12K and N60K (Model 4: Kendall & Monroe) had the worst predictive power for the POLYOX™ N60K and 301 blends. This observation suggests not a single model has superior predictive power over any other model when it comes to estimating the blend viscosities of POLYOX™ N60K with its higher (301) and lower (N12K) viscosity grades.

For these two batches of POLYOX™ N60K and 301, the blend of 80% N60K plus 20% of 301 met the upper specification target viscosity of ~4000 mPa.s. Models 3 (Refutas) and 5 (Bingham) each deviated from the actual viscosity by +/-10%. The average of these two models would have precisely predicted the blend viscosity of the 80/20 ratio of POLYOX™ N60K/301.

POLYOX™ WSR N60K LEO NF	POLYOX™ WSR 301 LEO NF	MODEL 1 VISCOSITY, MPA.S	MODEL 2 VISCOSITY, MPS.S	MODEL 3 VISCOSITY, MPA.S	MODEL 4 VISCOSITY, MPA.S	MODEL 5 VISCOSITY, MPA.S	ACTUAL VISCOSITY, MPA.S
0	100	N/A	N/A	N/A	N/A	N/A	26,000* (3760**)
50	50	8653	9331	8093	10541	5186	6700
60	40	6944	7476	6515	8473	4470	5970
80	20	4472	4706	4289	5184	3503	3900
90	10	3589	3696	3506	3920	3161	3280
100	0	N/A	N/A	N/A	N/A	N/A	2880

Table 6. POLYOX™ N60 with POLYOX™ 301 at 2% solution Spindle 3, rpm 10, min one

*Estimated two wt% viscosity for POLYOX™ 301

**COA value at 1% polymer concentration for POLYOX™ 301

POLYOX™ WSR N60K LEO NF	POLYOX™ WSR N12K LEO NF	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
0	100	N/A	N/A	N/A	N/A	N/A
50	50	29	39	21	57	-23
60	40	16	25	9	42	-25
80	20	15	21	10	33	-10
90	10	9	13	7	20	-4
100	0	N/A	N/A	N/A	N/A	N/A

Table 7. Percent deviation of model predictions from actual blend viscosity

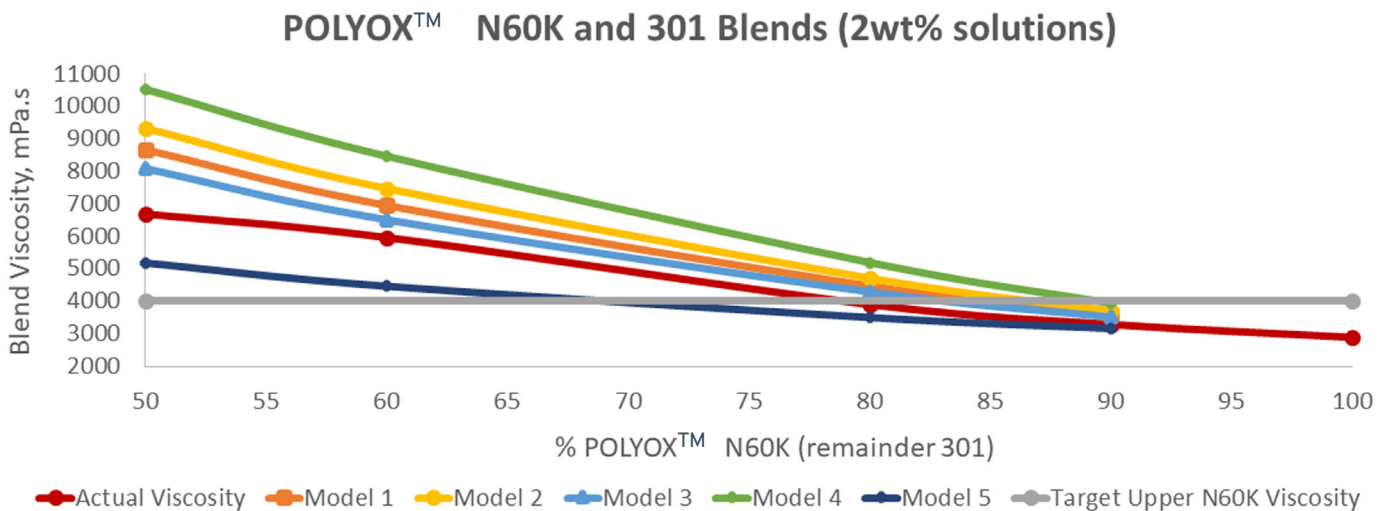


Figure 3. Predicted (Models 1-5) and actual (red curve) viscosities of POLYOX™ N60K and 301 batches.

BLEND OF POLYOX™ COAGULANT WITH POLYOX™ 303

A second case study aimed to target the viscosity specification extremes of POLYOX™ Coagulant (one wt% solutions): 7,500 mPa.s is the upper limit and 5,500 mPa.s is the lower limit. By blending in the next higher viscosity grade, POLYOX™ 303 (viscosity is also measured at one wt% solution), with the Coagulant grade, we can target the upper spec. In the case here, the starting Coagulant viscosity was below the lower specification limit, which can occur when the sample is stored past the retest date. The POLYOX™ 303 batch's starting viscosity of 7780 mPa.s was near the 7,500 mPa.s target, therefore only minimal amount of Coagulant was required to reach 7,500 mPa.s. The actual blend viscosity data showed a blend of 85% POLYOX™ 303 with 15% Coagulant obtained a solution viscosity of 7,400 mPa.s., closely approximating the viscosity target of 7,500 mPa.s.

All models closely predicted the blend viscosity (Table 8 and Figure 4). Deviations from the actual viscosity were less than 5% (Table 9), suggesting all models could be used to accurately predict the blends of POLYOX™ 303 and Coagulant at ratios of 75/25 to 85/15 (303/Coagulant). As demonstrated in the POLYOX™ N60K/ N12K case study, all models underestimated the measured viscosity, which is a useful consideration when implementing these models for QbD.

POLYOX™ WSR COAGULANT NF	POLYOX™ WSR 303 LEO NF	Model 1 Viscosity, mPa.s	Model 2 Viscosity, mPa.s	Model 3 Viscosity, mPa.s	Model 4 Viscosity, mPa.s	Model 5 Viscosity, mPa.s	Actual Viscosity, mPa.s
0	100	N/A	N/A	N/A	N/A	N/A	7780
15	85	7295	7305	7285	7322	7200	7400
20	80	7139	7152	7127	7174	7025	7300
25	75	6987	7002	6973	7027	6859	7120
100	0	N/A	N/A	N/A	N/A	N/A	5060

Table 8. POLYOX™ COAG with POLYOX™ 303 at 1% solution Spindle 2, rpm 2, min 5

% Deviation from Actual Viscosity						
POLYOX™ WSR COAGULANT NF	POLYOX™ WSR 303 LEO NF	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
0	100	N/A	N/A	N/A	N/A	N/A
15	85	-1	-1	-2	-1	-3
20	80	-2	-2	-2	-2	-4
25	75	-2	-2	-2	-1	-4
100	0	N/A	N/A	N/A	N/A	N/A
100	0	N/A	N/A	N/A	N/A	N/A

Table 9. Percent deviation of model predictions from actual blend viscosity

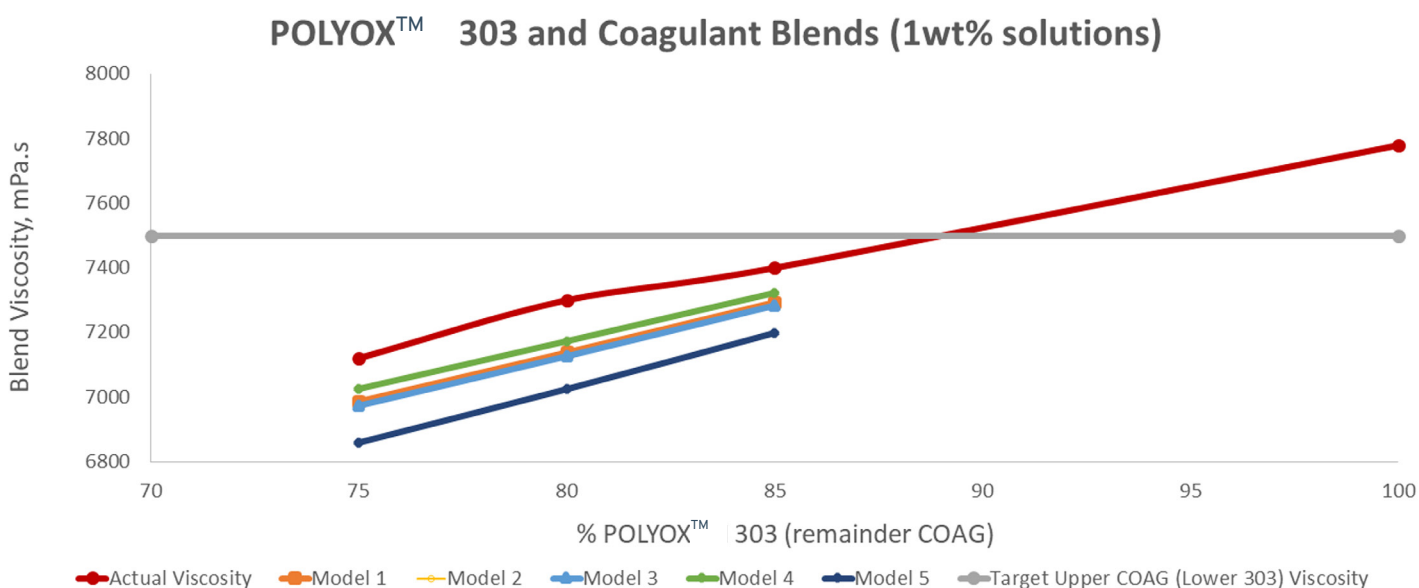


Figure 4. Predicted (Models 1-5) and actual (red curve) viscosities of POLYOX™ Coagulant and 303 batches.

BLEND OF POLYOX™ COAGULANT WITH POLYOX™ 301

The final blend combination of POLYOX™ Coagulant and 301 was used in a client case study. The client requested a blend viscosity of 6,000 mPa.s. The models were first used to estimate the amount of POLYOX™ Coagulant (a new batch with measured viscosity of 6140 mPa.s) needed to achieve 6,000 mPa.s when blended with a new batch of POLYOX™ 301 (3360 mPa.s). The models all estimated 96 to 97 wt% Coagulant would be needed (301 making up the remainder wt%, Table 10). Knowing that the models trend towards the low end, the team chose to make solutions of 97 wt% Coagulant and three wt% 301 to target the 6,000 mPa.s. In addition, the team made 90 wt% Coagulant and 10 wt% 301 to further test the accuracies of the models with this blend system.

Individual Viscosity, mPa.s			Predicted wt % of Coagulant in blend to hit 6,000 mPa.s			
POLYOX™ WSR COAGULANT NF	POLYOX™ WSR 303 LEO NF	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
6140	3360	96.2	96.0	96.3	95.8	97.2

Table 10. Predicted wt% of POLYOX™ Coagulant needed to hit blend viscosity of 6,000 mPa.s

All models accurately predicted the blend viscosity of 97 wt% POLYOX™ Coagulant with three wt% POLYOX™ 301 (Table 11 and Figure 5). The measured viscosity of the resulting blend was 6,020 mPa.s., achieving the target of 6,000 mPa.s. Each model was within 30 mPa.s (less than 1% error, Table 12) of the measured viscosity, indicating all models accurately predict the blend viscosity of these two materials at this ratio. The models one through four had slightly higher errors (2% error) for the 90/10 blend, which measured at 5,680 mPa.s, compared to the errors for the 97/3 blend (<0.5% error). Model five slightly improved its predictive power at the 90/10 blend (-0.2% error) than at the 97/3 blend (-0.5% error).

POLYOX™ WSR COAGULANT NF	POLYOX™ WSR 301 LEO NF	Model 1 Viscosity, mPa.s	Model 2 Viscosity, mPa.s	Model 3 Viscosity, mPa.s	Model 4 Viscosity, mPa.s	Model 5 Viscosity, mPa.s	Actual Viscosity, mPa.s
0	100	N/A	N/A	N/A	N/A	N/A	3360
90	10	5781	5792	5769	5811	5671	5680
97	3	6030	6034	6026	6040	5991	6020
100	0	N/A	N/A	N/A	N/A	N/A	6140

Table 11. POLYOX™ Coagulant with POLYOX™ 301 at 1% solution Spindle two, rpm two, min five

% Deviation from Actual Viscosity						
POLYOX™ WSR COAGULANT NF	POLYOX™ WSR 301 LEO NF	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5
0	100	N/A	N/A	N/A	N/A	N/A
90	10	2	2	2	2	-0.2
97	3	0.2	0.2	0.1	0.3	-0.5
100	0	N/A	N/A	N/A	N/A	N/A

Table 12. Percent deviation of model predictions from actual blend viscosity

POLYOX™ Coagulant and 301 Blends (1wt% solutions)

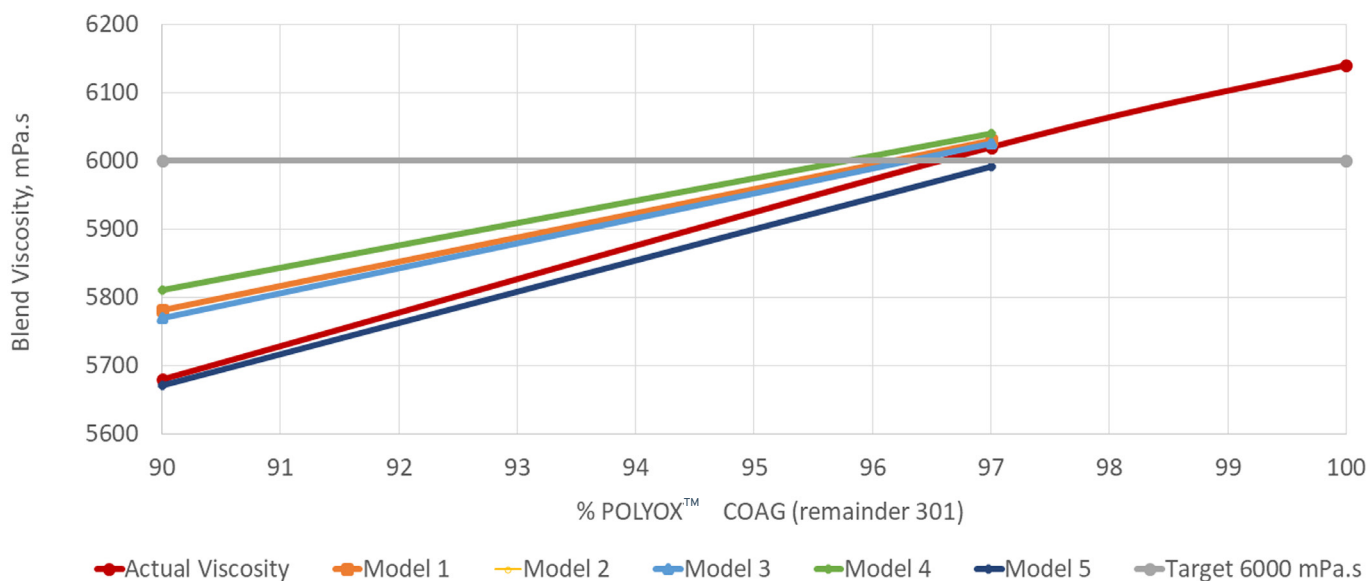


Figure 5. Predicted (Models 1-5) and actual (red curve) viscosities of POLYOX™ Coagulant and 301 batches.

DISCUSSION & CONCLUSION

The data show that out of the five models tested, there is not a single model that consistently outperforms the other models in predicting the blend viscosity of high molecular weight POLYOX™ polyethylene oxide grades. In two cases evaluating blends of the high MW POLYOX™ PEO grade of Coagulant with either 301 or 303 (also high MW grades), all models predicted the viscosities at the tested ratios with high accuracy. Any of the models therefore could be used for future estimation of blend ratios of these grades for a given viscosity target.

However, the models did not always perform similarly when blending of the middle MW grade of N60K with either N12K or 301. Large deviations from the actual viscosity and even from the other predicted viscosities were observed when the blend ratios were greater between 20/80 and 80/20. When one grade dominated the blend (>80 wt%), the models had less error from the actual viscosity than when the two components were mixed close to 50/50 ratio. Since this study did not look at 50/50 blends of the highest MW POLYOX™ PEO grades, this trend could also be true for the blends of Coagulant with either 301 or 303. Although a potential weakness in applying the models to predicting POLYOX™ PEO viscosity blends, one is not likely to combine two grades near 50/50 ratio as part of a QbD approach. In most cases, to target the upper or lower viscosity specification of a given grade, the blend ratios will likely comprise >80% of one grade, as the data here also show.

In summary, the use of blending models streamlines the process by reducing the need for exhaustive trial-and-error combinations to target a desired viscosity. It empowers researchers with a tool to expedite their QbD approach in the creation of robust and safe formulations. For support using blending models please reach out to the Pharma Solutions technical team, who will be happy to assist.



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