

# Pharmaceutical Excipients Case Study

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**CONFIDENTIAL**

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The following test was performed:

1. Standardized Gel Permeation Chromatography (GPC)

## Objective

The goal of this study was to demonstrate the importance of GPC in the analysis of commercially available pharmaceutical excipient materials. Herein, 7 pharmaceutical excipient polymers, namely Chitosan, hypromellose, polyacrylic acid, alginic acid, polycaprolactone, polyvinylpyrrolidone, and xanthan gum were analyzed by standardized Gel Permeation Chromatography (GPC), an analytical service offered at Jordi Labs.

## Summary of Results

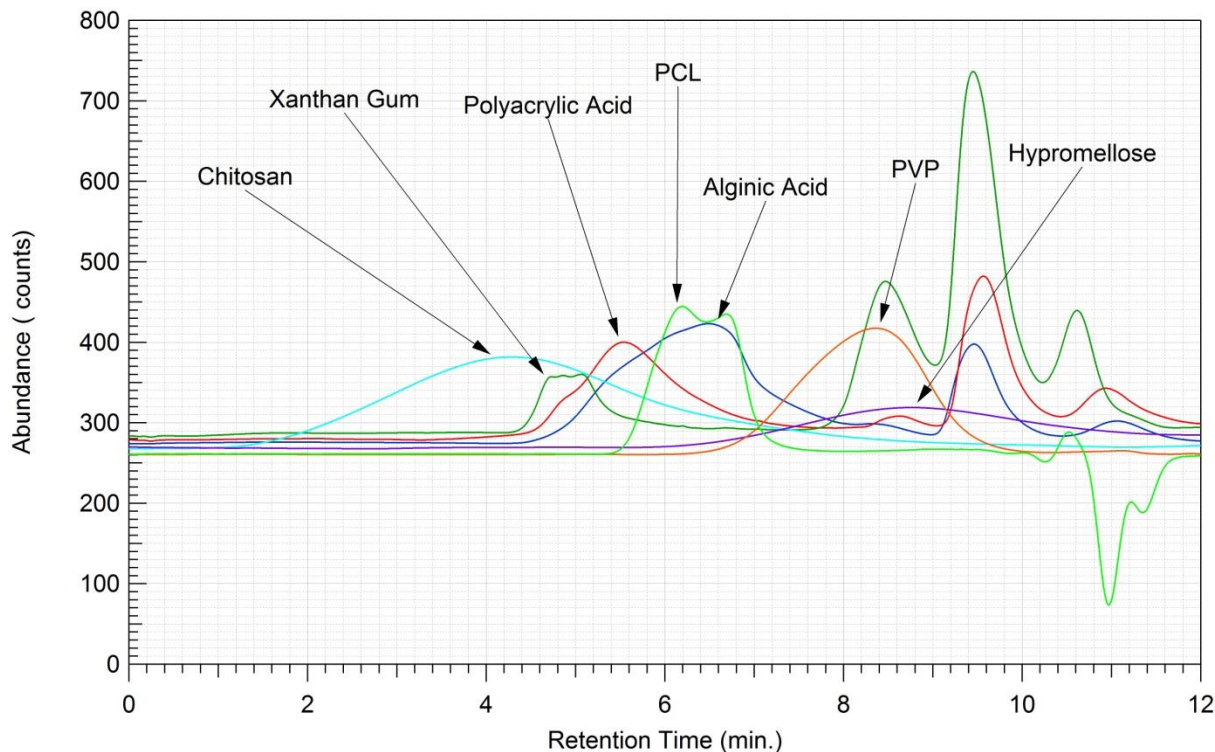
Seven (7) pharmaceutical excipient polymers were analyzed by GPC. The results are summarized in **Table 1-Table 7**.

## Background

Apart from active ingredients, inactive excipients play a significant role in formulation development of pharmaceuticals. Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug, which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. Although technically "inactive" from a therapeutic perspective, pharmaceutical excipients are critical and essential components of a modern drug product. In many products, excipients make up the bulk of the total dosage form.

Some excipients are used to keep the drug from being released too early in the assimilation process in places where it could damage tender tissue and create gastric irritation or upset the stomach. Other excipients can disintegrate quickly in aqueous/physiological medium releasing incorporated active pharmaceutical ingredients within seconds, and are used to protect the product's stability so it will be at maximum effectiveness at the time of use. Excipients are also used to improve the product's taste or look, which enhances patient compliance, especially in children.

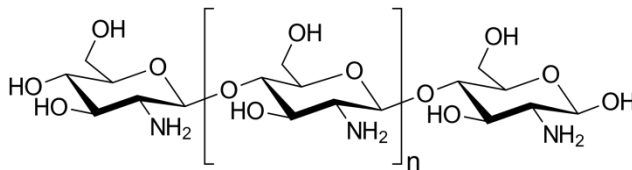
Gel permeation chromatography (GPC), an analytical technique for the determination of the molecular weight distribution of polymers (**Figure 1**), can be used to study pharmaceutical excipient polymers by determining the rate at which a polymeric material might decompose as part of accelerated aging studies.



**Figure 1.** Overlay of pharmaceutical excipient polymers in this study

## 1. Chitosan

**Chitosan**, a pharmaceutical excipient material and a linear polysaccharide, is composed of randomly distributed  $\beta$ -(1 $\rightarrow$ 4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It can be derived by partial deacetylation of chitin from crustacean shells.<sup>1,2</sup>



**Figure 2.** The chemical structure of Chitosan

<sup>1</sup> Illum L.: Pharm. Res. 15, 1326 (1998)

<sup>2</sup> Jones D.S., Mawhinney H.J.: Chitosan. In: Rowe, R.C., Sheskey, P.J., Owen, S.C., Eds., Handbook of Pharmaceutical Excipients, fifth edn., pp. 159-162, American Pharmaceutical Association and The Pharmaceutical Press, Washington DC 2006

Chitosan is reported as being under investigation for use in a number of pharmaceutical formulations. Although chitosan is not used as a pharmaceutical excipient in any marketed drug yet, established human exposure to chitosan has occurred through its use as a dietary supplement in preparations for obesity and hypercholesterolemia.<sup>3, 4</sup>

A range of studies have shown that chitosan acts as a hemostatic agent.<sup>5</sup> In addition, it has been suggested that when chitosan dissolves in the stomach, it can emulsify fat and form a gel in the intestine which entraps fat and prevents intestinal absorption.<sup>6, 7</sup>

### Sample Preparation

A chitosan sample was dissolved into water with 0.6 M acetic acid and 0.01 NaNO<sub>3</sub>. The resulting solution was agitated overnight at room temperature, yielding a transparent solution. The sample was then analyzed without further preparation.

### Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in **Table 1**. The resulting weight fraction below 1 kDa is also presented in **Table 1**. The refractive index chromatogram is presented in **Figure 3**.

**Table 1**

Actual Mw Unknown

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	Weight % < 1000 Da
Chitosan (Relative to PSAC)	53,378	809,608	2,628,189	15.17	0.17

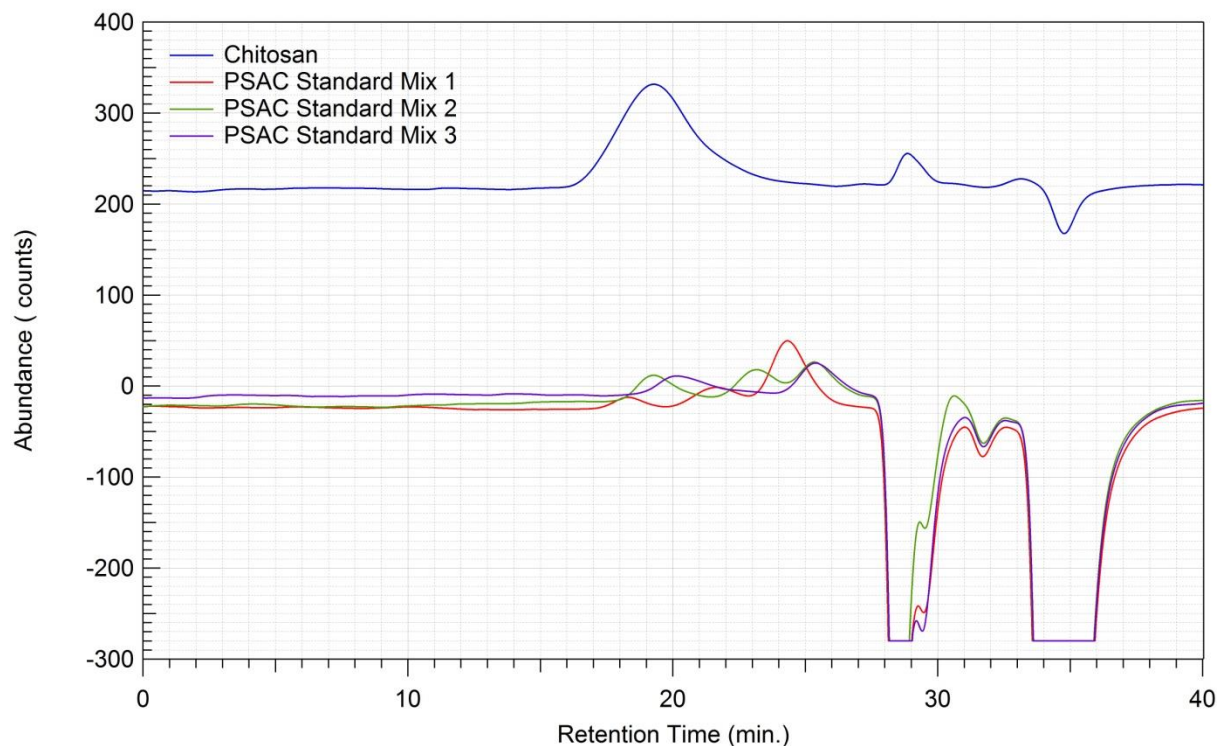
<sup>3</sup> Illum L.: Pharm. Res. 15, 1326 (1998)

<sup>4</sup> Martindale: The Complete Drug Reference, 35th edn., Sweetman, S.C., Ed., Pharmaceutical Press, London 2007

<sup>5</sup> Mathews S., Kaladhar K., Sharma C.P.: J. Biomed. Mater. Res. 79A, 147 (2006)

<sup>6</sup> Kaats G.R., Michalek J.E., Preuss H.G.: J. Am. Coll. Nutr. 25, 389 (2006)

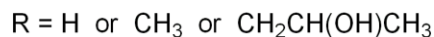
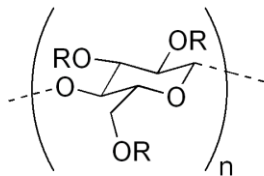
<sup>7</sup> Ylitalo R., Lehtinen S., Wuolijoki E., Ylitalo P., Lehtimäki T.: Arzneimittelforschung 52, 1 (2002)



**Figure 3.** Refractive index (RI) chromatogram of chitosan

## 2. Hypromellose

**Hypromellose** is a semisynthetic, inert, viscoelastic polymer used as eye drops, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.



**Figure 4.** Chemical structure of hypromellose

Hypromellose has been used as an excipient in oral tablets and capsule formulations. It can act as a controlled release agent to regulate the release of a medicinal compound into the digestive tract.<sup>8,9</sup>

<sup>8</sup> Reddy, Indra K.; Riža Mihvar (2004). Chirality in Drug Design and Development

<sup>9</sup> Niazi, Sarfaraz (2004). Handbook of Pharmaceutical Manufacturing Formulations

## Sample Preparation

A hypromellose sample was dissolved into water with 0.6 M acetic acid and 0.01 NaNO<sub>3</sub>. The resulting solution was agitated overnight at room temperature, yielding a transparent solution. The sample was then analyzed without further preparation.

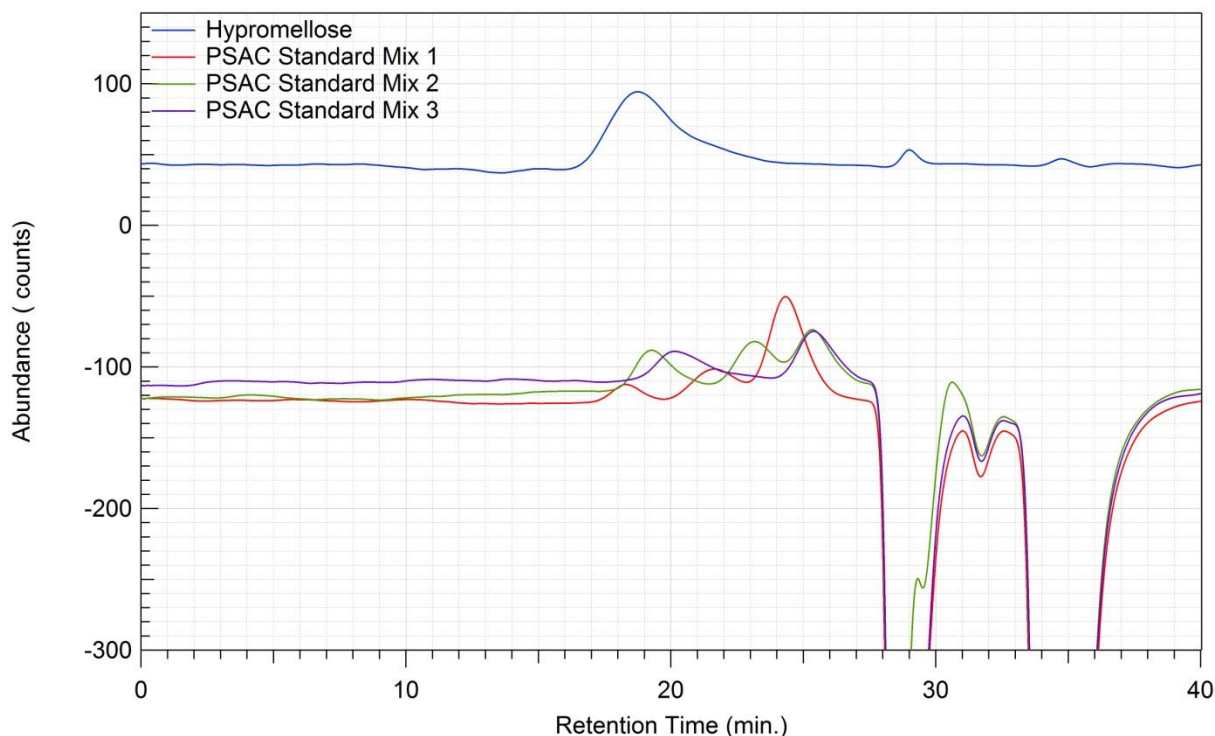
## Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in **Table 2**. The resulting weight fraction below 1 kDa is also presented in **Table 2**. The refractive index chromatogram is presented in **Figure 5**.

**Table 2**

Actual Mw Unknown

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	Weight % < 1000 Da
Hypromellose (Relative to PSAC)	11,058	874,850	2,457,757	79.11	2.03

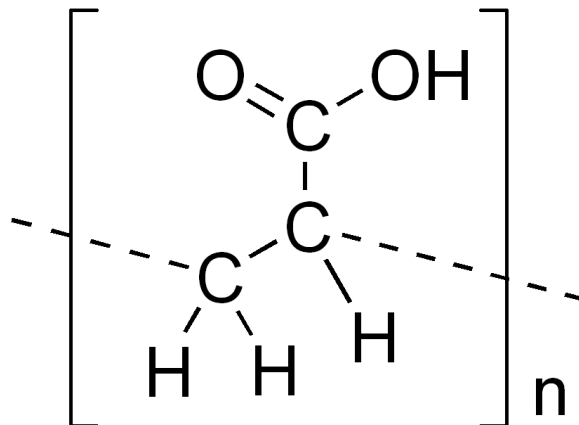


**Figure 5.** Refractive index (RI) chromatogram of hypromellose



### 3. Polyacrylic Acid

**Polyacrylic acid (PAA)** is a synthetic high-molecular weight polymer of acrylic acid. PAA is commercially prepared by free radical polymerization of the acrylic acid with thermochemical initiators such as potassium persulfate and AIBN.



**Figure 6.** Chemical structure of PAA

PAA is ideal for ocular delivery of ribozymes to the corneal epithelium as a drug delivery vehicle. Carbopol 974 and Pemulen TR1, two common high molecular weight polyacrylic acid polymers, have been used for ocular delivery of Ribosomes.<sup>10</sup> Polyacrylic acid based polymers are also used for oral and mucosal contact applications such as controlled release tablets, oral suspensions and bioadhesives.<sup>11</sup>

#### Sample Preparation

A PAA sample was dissolved into water with 0.2 M NaNO<sub>3</sub> and 0.01M Na<sub>2</sub>HPO<sub>4</sub>. The resulting solution was agitated overnight at room temperature, yielding a transparent solution. The sample was then analyzed without further preparation.

#### Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in

**Table 3.** The resulting weight fraction below 1 kDa is also presented in

**Table 3.** The refractive index chromatogram is presented in **Figure 7.**

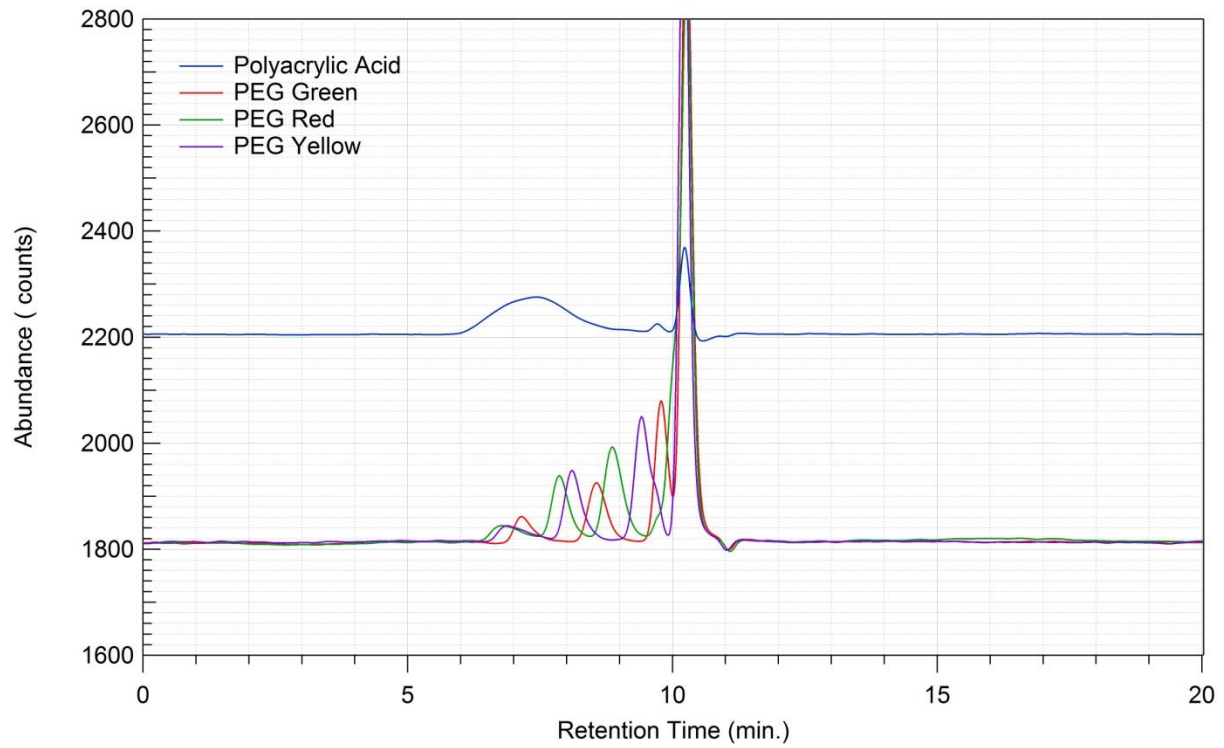
<sup>10</sup> Ayers, D.; Cuthbertson, J.M.; Schroyer, K.; Sullivan, S.M: J. Control. Release 1996, 38, 167-175

<sup>11</sup> Lubrizol Pharmaceutical Bulletin 1; Lubrizol: Wickliffe, OH, USA, 11 August 2010

**Table 3**

Actual  $M_v$  450,000 Da

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	Weight % < 1000 Da
Polyacrylic Acid (Relative to PEG)	123,872	1,075,561	9,386,225	8.68	N.D.

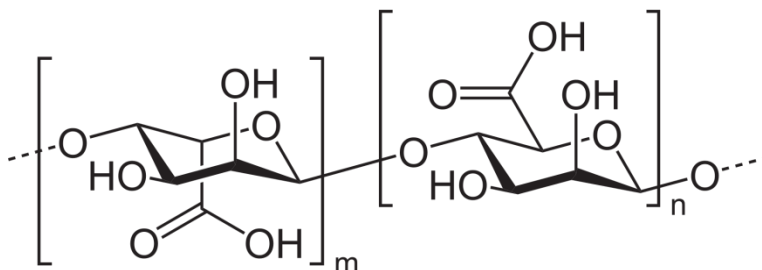


**Figure 7.** Refractive index (RI) chromatogram of polyacrylic acid



## 4. Alginic Acid

**Alginic acid** is a natural carbohydrate that comes from algae in seaweed (kelp) and is used in certain medications, such as Gaviscon liquid, to create a foam barrier for coating the stomach. Alginic acid is often combined with aluminum hydroxide and magnesium carbonate to form antacids.



**Figure 8.** Chemical structure of alginic acid

Alginic acid does not appear to be absorbed or metabolized after ingestion. In tablet and capsule formulations, alginic acid is used as both a binder and disintegrating agent at concentrations of 1–5% w/w.<sup>(1,2)</sup><sup>12, 13</sup> Alginic acid is also widely used as a thickening and suspending agent in a variety of pastes, creams, and gels; and as a stabilizing agent for oil-in-water emulsions.

### Sample Preparation

An alginic sample was dissolved into water with 0.2 M NaNO<sub>3</sub> and 0.01M Na<sub>2</sub>HPO<sub>4</sub>. The resulting solution was agitated overnight at room temperature, yielding a transparent solution. The sample was then analyzed without further preparation.

### Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in **Table 4**. The resulting weight fraction below 1 kDa is also presented in **Table 4**. The refractive index chromatogram is presented in **Figure 9**.

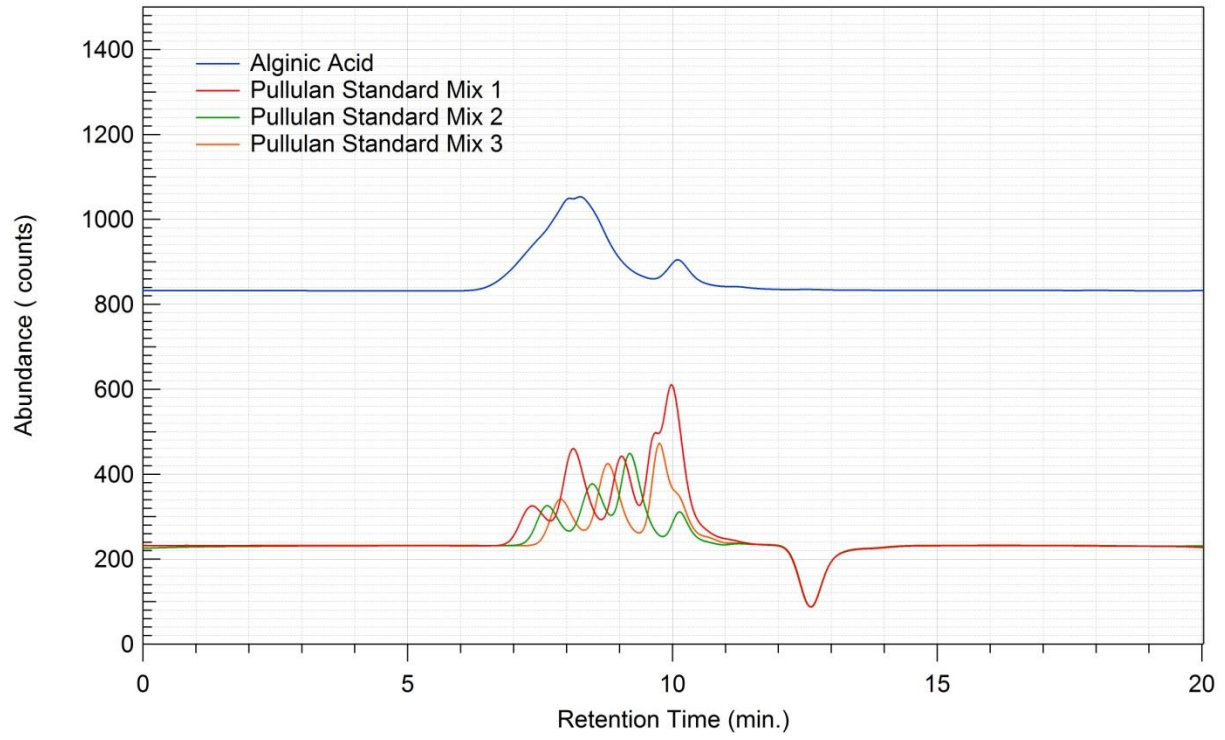
**Table 4**

Actual Mw Unknown

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	Weight % < 1000 Da
Alginic Acid (Relative to Pullulan)	26,374	455,026	3,753,983	17.25	N.D.

<sup>12</sup> Shotton E, Leonard GS: J Pharm Sci 1976; 65: 1170–1174

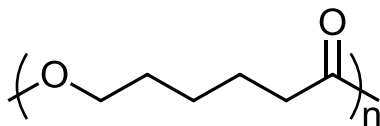
<sup>13</sup> Esezobo S: Int J Pharm 1989; 56: 207–211



**Figure 9.** Refractive index (RI) chromatogram of alginic acid

## 5. Polycaprolactone

**Polycaprolactone (PCL)** is a biodegradable aliphatic polyester that has a repeat unit of a pentyl group attached to an ester functional group (Figure 10). PCL is commercially prepared by the ring opening polymerization of the cyclic caprolactone monomer in the presence of a metal catalyst such as tin(II)octoate.



**Figure 10.** Chemical structure of PCL

Relative to other biodegradable aliphatic polyesters, PCL takes longer to degrade under environmental and physiological conditions due to its reduced ester bond density along the polymer chain.<sup>14</sup> As a result, PCL is more preferable for use in long-term implantable delivery devices. PCL is widely used in scaffold materials in tissue engineering, and in the delivery of both hydrophobic drugs such as cisplatin, doxycycline, and carboplatin, and hydrophobic drugs such as paclitaxel, ketoprofen, cannabinoid, and many more.<sup>14</sup>

### Sample Preparation

A PCL sample was dissolved into THF overnight. The resulting solution was agitated overnight at room temperature, yielding a transparent solution. The sample was then analyzed using a **Jordi Resolve DVB Mixed Bed** column without further preparation.

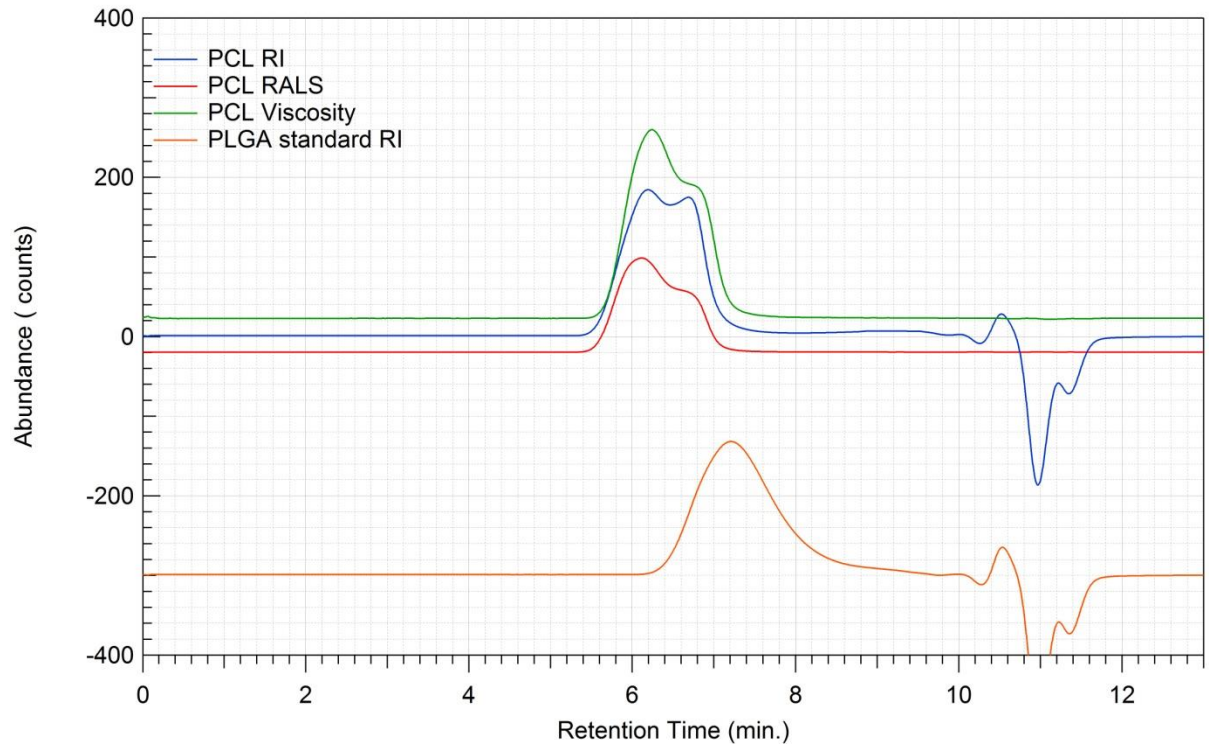
### Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in **Table 5**. The resulting weight fraction below 1 kDa is also presented in **Table 5**. The refractive index chromatogram is presented in **Figure 11**.

**Table 5**  
Actual  $M_n$  80,000 Da

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	IV (dL/g)	Rh (nm)	Weight % < 1000 Da
PCL (Relative to PMMA)	82,736	156,597	274,297	1.83	N/A	N/A	0.918
PCL (Absolute, GPC-T)	82,003	116,678	162,005	1.43	1.00	11.93	0.00

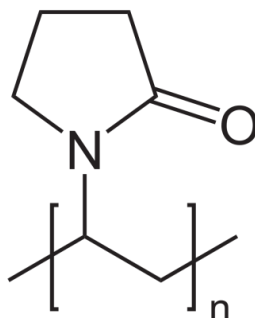
<sup>14</sup> Malikhhammadov, E., Tanir, T. E., Kiziltay, A., Hasirci, V., & Hasirci, N. (2017). *PCL and PCL-based materials in biomedical applications. Journal of Biomaterials Science, Polymer Edition*, 29(7-9), 863–893.



**Figure 11.** Refractive index (RI) chromatogram of polycaprolactone

## 6. Polyvinylpyrrolidone (PVP)

**Polyvinylpyrrolidone (PVP)** is a water-soluble polymer made from the monomer N-vinylpyrrolidone (**Figure 12**).



**Figure 12.** Chemical structure of PVP

It is used as a binder in many pharmaceutical tablets, a film former for ophthalmic solutions, a flavor agent in liquid and chewable tablets, and as an adhesive for transdermal systems; it simply passes through the body when taken orally. PVP formulations are widely used in the pharmaceutical industry due to their ability to dissolve in both water and oil solvents. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

### Sample Preparation

A PVP sample was dissolved into water and methanol (50/50). The resulting solution was agitated overnight at room temperature, yielding a transparent solution. The sample was then analyzed without further preparation.

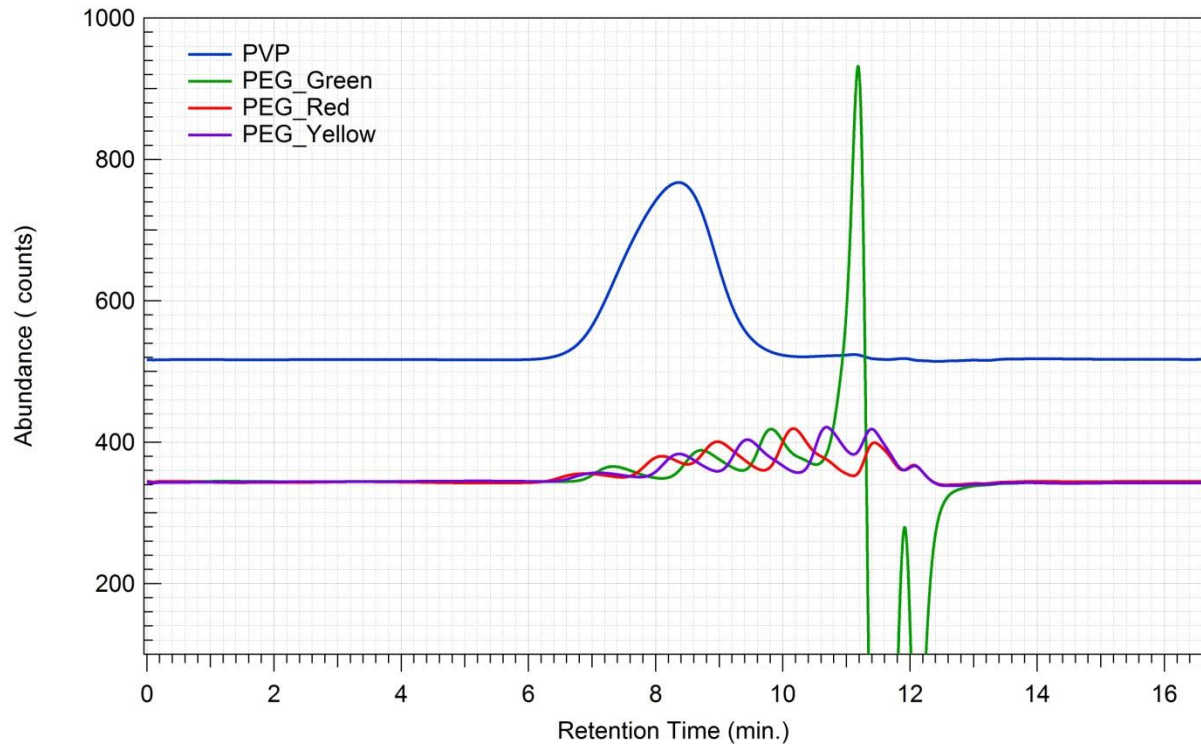
### Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in **Table 6**. The resulting weight fraction below 1 kDa is also presented in **Table 6**. The refractive index chromatogram is presented in **Figure 13**.

**Table 6**

Actual  $M_n$  unknown

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	Weight % < 1000 Da
PVP (Relative to PEG)	6,667	190,276	583,781	28.54	1.78

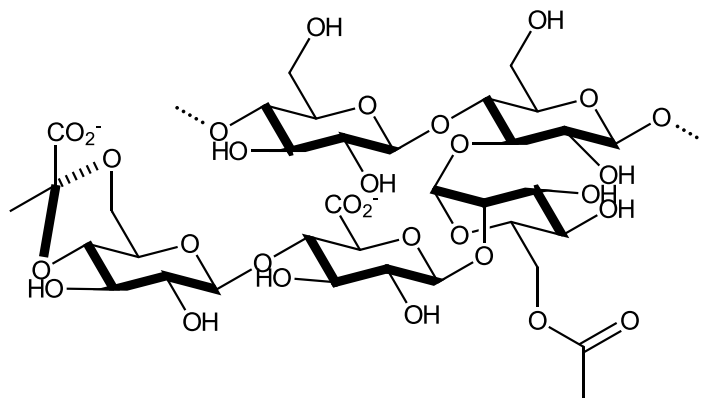


**Figure 13.** Refractive index (RI) chromatogram of polyvinylpyrrolidone



## 7. Xanthan Gum

Xanthan gum is a polysaccharide with a repeat unit of five sugar residues: two glucose residues, two mannose residues, and one glucuronic acid residue. The polymer backbone consists of four  $\beta$ -D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose.



**Figure 14.** Chemical structure of xanthan gum

Xanthan gum is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. It is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent.

Xanthan gum has been used as a suspending agent for conventional, dry and sustained-release suspensions. Xanthan gum has shown synergistic rheological effects when mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums. In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1:2 and 1:9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum and guar gum ratios between 3:7 and 1:9. Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets.

### Sample Preparation

A xanthan gum sample was dissolved into water with 0.2 M  $\text{NaNO}_3$  and 0.01M  $\text{Na}_2\text{HPO}_4$ . The resulting solution was agitated overnight at room temperature, yielding a milky solution. The sample was then filtered using a laminated PTFE filter paper and analyzed without further preparation.

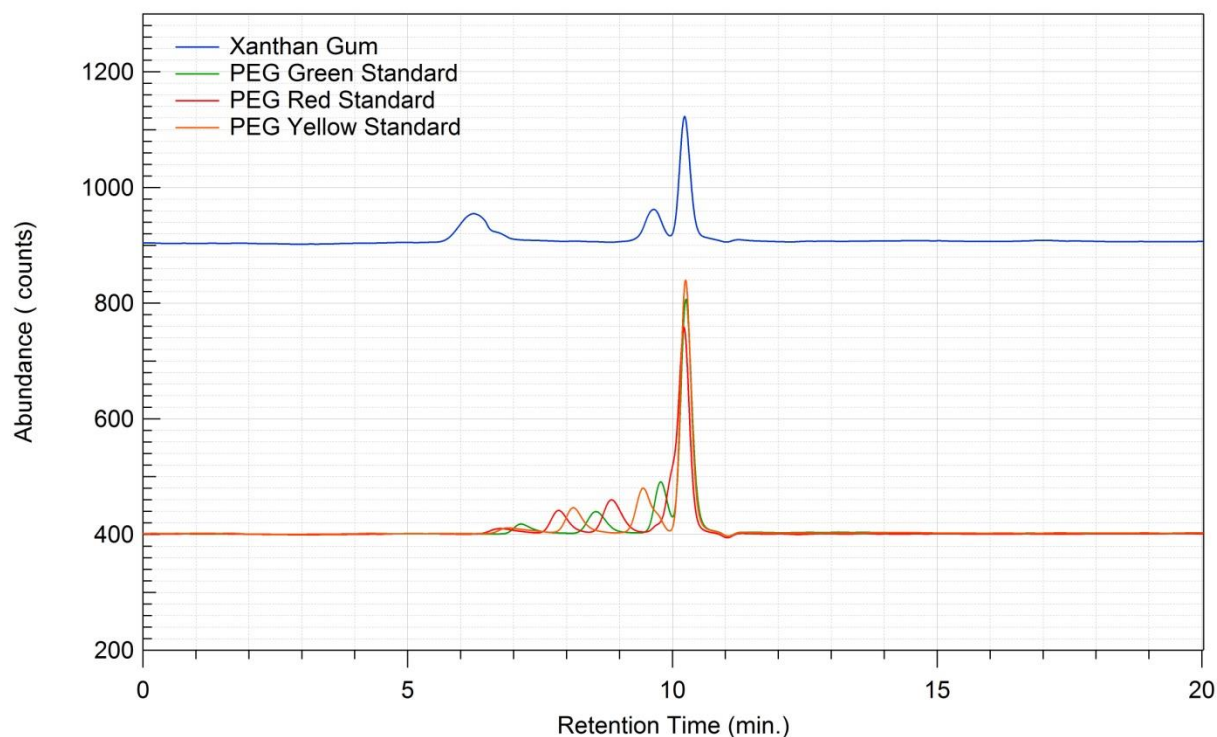
## Results

The calculated molecular weight averages ( $M_n$ ,  $M_w$ ,  $M_z$ ) and dispersity values (PDI) are presented in **Table 7**. The resulting weight fractions below 1 kDa are also presented in **Table 7**. The refractive index chromatogram is presented in **Figure 15**.

**Table 7**

Actual  $M_n$  Unknown

Polymer	$M_n$ (Da)	$M_w$ (Da)	$M_z$ (Da)	PDI	Weight % < 1000 Da
Xanthan gum (Relative to PEG)	2,501,714	8,129,801	17,742,516	3.25	0



**Figure 15.** Refractive index (RI) chromatogram of Xanthan Gum

## Closing Comments

Jordi Labs' reports are issued solely for the use of the clients to whom they are addressed. No quotations from reports or use of the Jordi name is permitted except as authorized in writing. The liability of Jordi Labs with respect to the services rendered shall be limited to the amount of consideration paid for such services and do not include any consequential damages.

Jordi Labs specializes in polymer analysis and has more than 35 years' experience performing regulatory, quality control and failure testing. We are one of the few labs in the United States specialized in this type of testing. We will work closely with you to help explain your test results and complete your project goals. We appreciate your business and are looking forward to speaking with you concerning these results.

Sincerely,

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