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Drug Delivery Polymers Case Study

Released by:

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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 drug delivery materials. Herein, 6 drug delivery polymers, namely Eudragit RS and RL, Eudragit L and S, Ethylcellulose, Cellulose Acetate, Poly(lactic-co-glycolic acid), and a PAMAM dendrimer were analyzed by standardized Gel Permeation Chromatography (GPC), an analytical service offered at Jordi Labs.

Summary of Results

Six (6) drug delivery polymers were analyzed by GPC. The results are summarized in

Table 1-**Table 5**.

Background

Pharmaceutical drugs are often restricted by their low solubility in physiological conditions, physical and chemical instability, toxicity, and other properties. Physical instability, for example, may cause modification of highly ordered protein structure, resulting in unwanted processes such as precipitation or aggregation.

Drug delivery polymers have played an important role in the development of drug delivery technologies by providing controlled release of therapeutic ingredients in constant doses over long periods, cyclic dosage, and tunable release of both hydrophilic and hydrophobic drugs.

From a drug delivery perspective, polymer devices can be categorized as diffusion-controlled (monolithic devices), solvent-activated (swelling- or osmotically-controlled devices), chemically controlled (biodegradable), or externally-triggered systems (e.g., pH, temperature). Some systems have been designed to provide safe passage for pharmaceuticals through inhospitable physiological regions. More advanced externally-triggered drug delivery systems allow the release of therapeutics to be triggered on demand and remotely by a physician or patient.

Molecular weight is an important parameter to tune the functions aforementioned. Gel permeation chromatography (GPC), an analytical technique for the determination of the molecular weight distribution of polymers (**Figure 1**), can be used to study drug delivery polymers by determining the rate at which a polymeric material might decompose as part of accelerated aging studies.

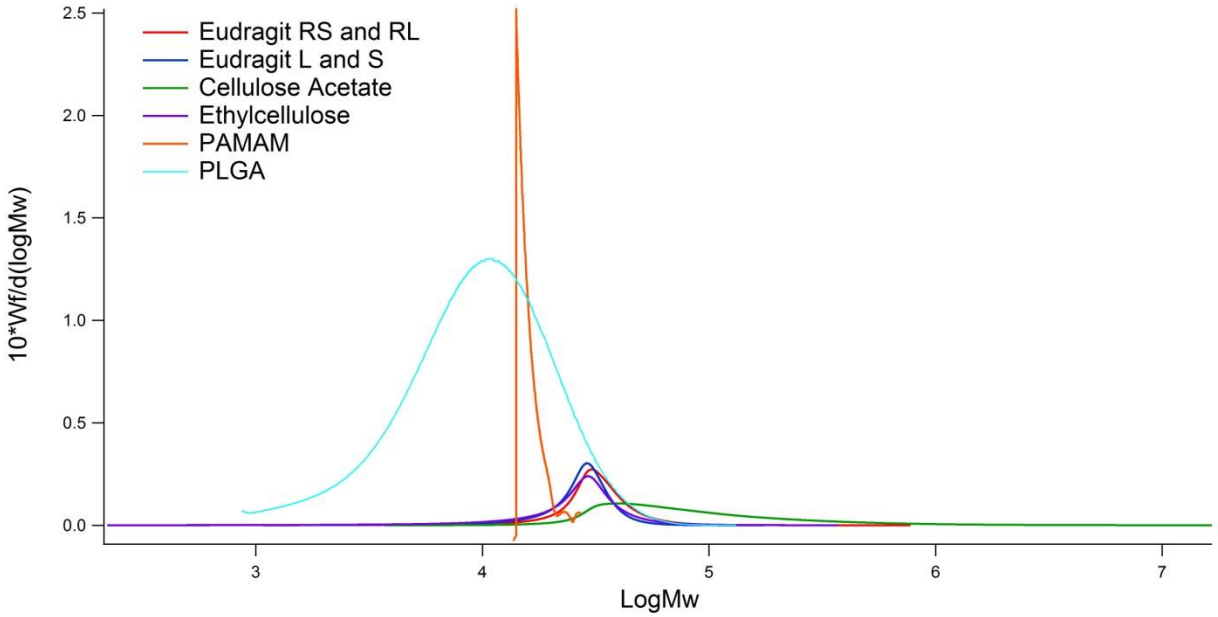

Figure 1. Overlay of drug delivery polymers in this study

1. Eudragit L and S & Eudragit RS and RL

Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid. Eudragit L and S is a copolymer based on methacrylic acid and methyl methacrylate whereas Eudragit RS and RL is based on methyl methacrylate, ethyl methacrylate and quaternary ammonium methyl methacrylate (ammonioalkyl methacrylate) monomers.

The physicochemical properties of Eudragit polymers are determined by the incorporated functional groups. For example, Eudragit L and S polymers are preferred when a drug must be protected from gastric acidic fluids, and delivered after reaching the intestine for maximum efficiency. This is normally referred to as delayed drug release. Eudragit RS and RL polymers, on the other hand, are preferred for time-controlled drug release due to the fact that they are water insoluble and pH-independent. The proportion of quaternary ammonium groups in

Eudragit RS and RL polymers play an important role of tuning the permeability of the polymer in digestive fluids.

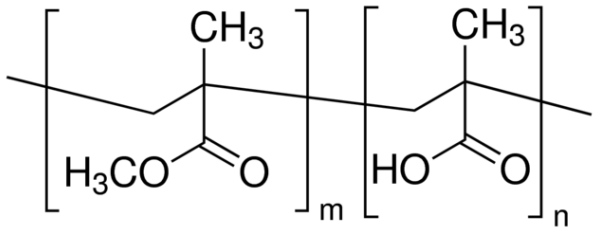

Figure 2. The chemical structure of Eudragit L and S
For L, m/n=1; and for S, m/n=1.2

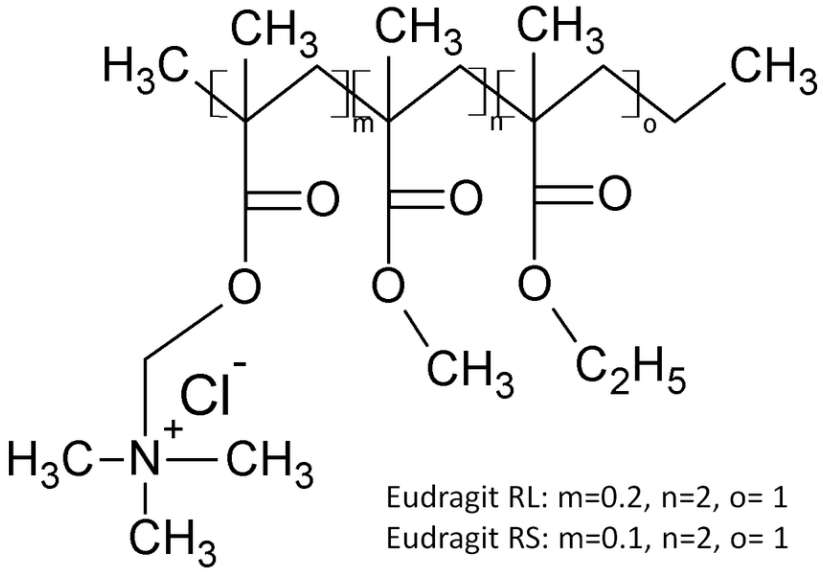

Figure 3. The chemical structure of Eudragit RS and RL

Sample Preparation

Eudragit polymer samples were dissolved into DMAc (Dimethylacetamide) with 0.1M LiBr. The resulting solutions were agitated overnight at room temperature, yielding transparent solutions. The samples were then analyzed on 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 1. The resulting weight fraction below 1 kDa is also presented in

Table 1. The refractive index chromatogram is presented in **Figure 4**-**Figure 7**.

Table 1

Actual Mw 34,000 Da (Eudragit L and S)
Actual Mw Unknown (Eudragit RS and RL)

Polymer	M_n (Da)	M_w(Da)	M_z (Da)	PDI	Weight % < 1000 Da
Eudragit L and S (Relative to PMMA)	14,043	28,952	44,690	2.06	0.17
Eudragit L and S (Relative to PSAC)	19,585	27,638	31,151	1.41	0.32
Eudragit RS and RL (Relative to PMMA)	23,511	41,687	66,472	1.77	N.D.
Eudragit L and S (Relative to PSAC)	22,747	32,793	40,373	1.44	0.12

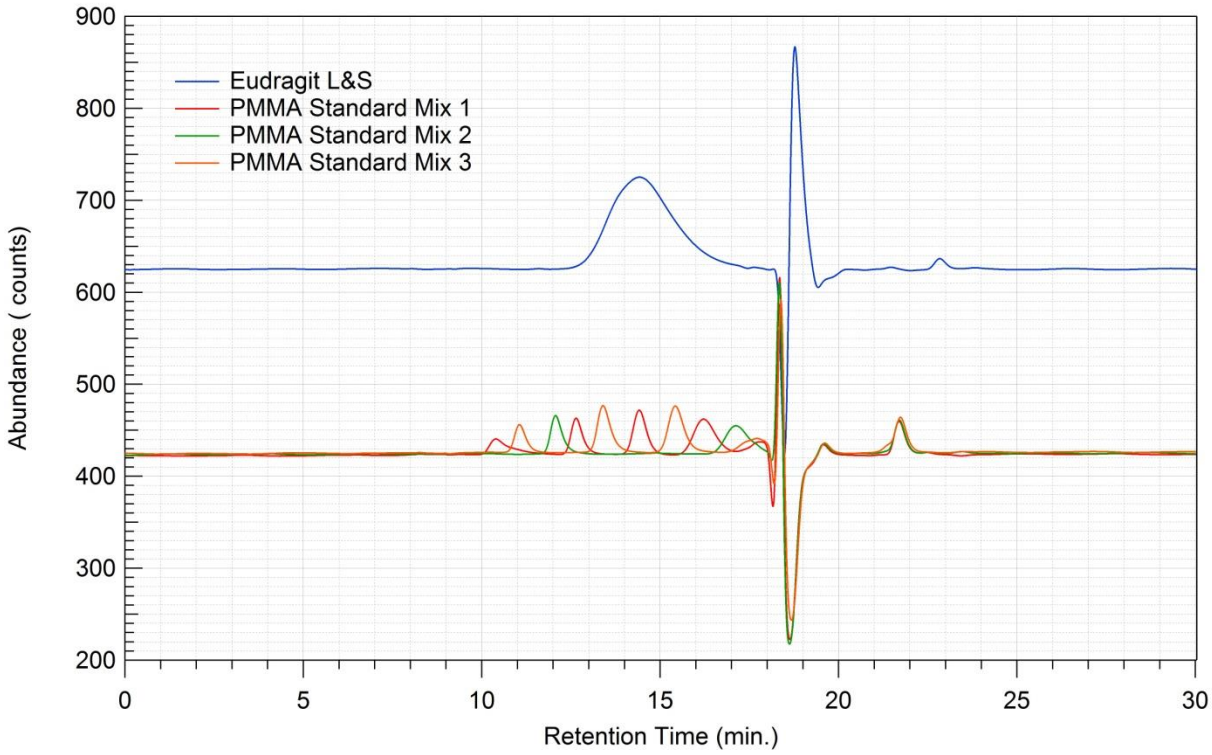

Figure 4. Refractive index (RI) chromatogram of Eudragit L and S (PMMA standard)

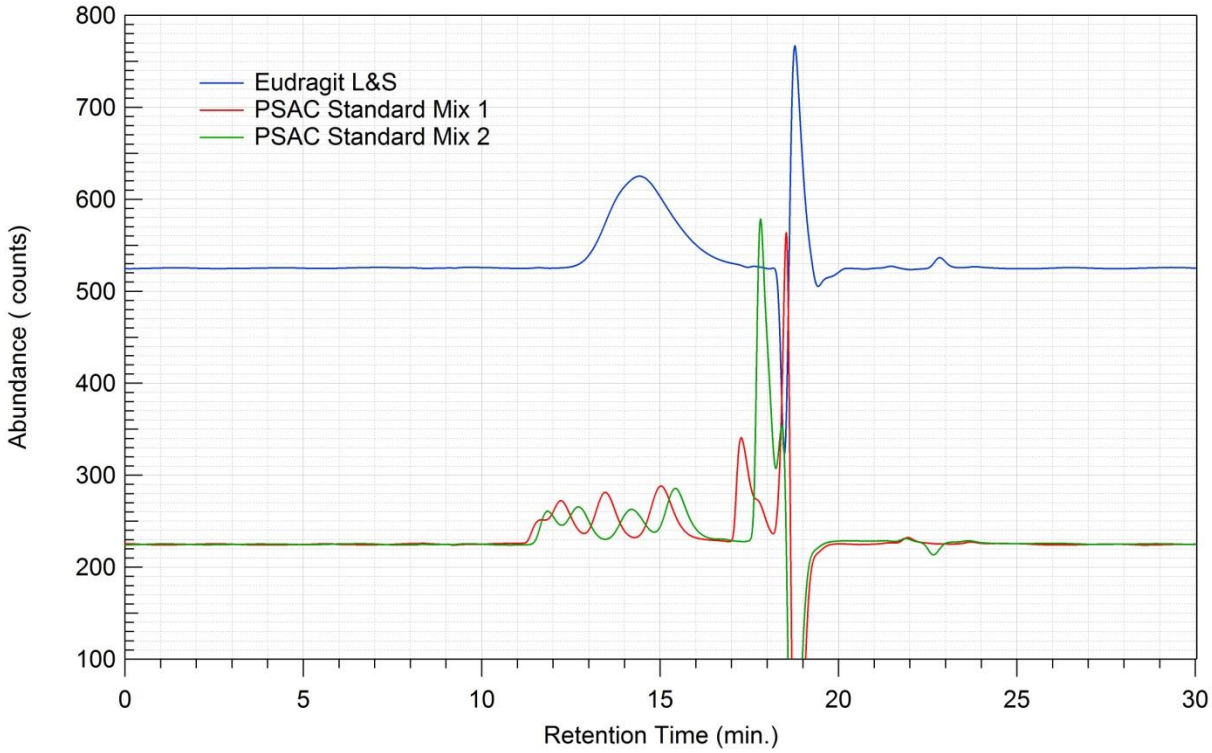

Figure 5. Refractive index (RI) chromatogram of Eudragit L and S (PSAC standard)

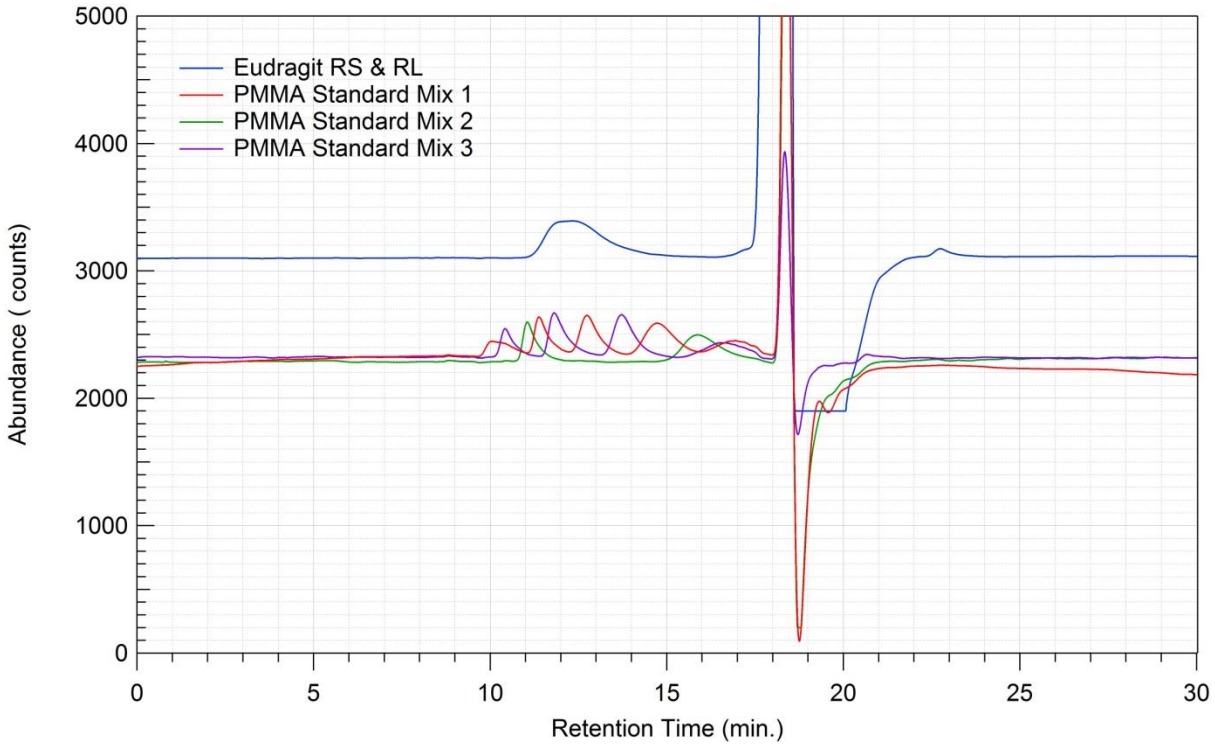

Figure 6. Refractive index (RI) chromatogram of Eudragit RS and RL (PMMA standard)

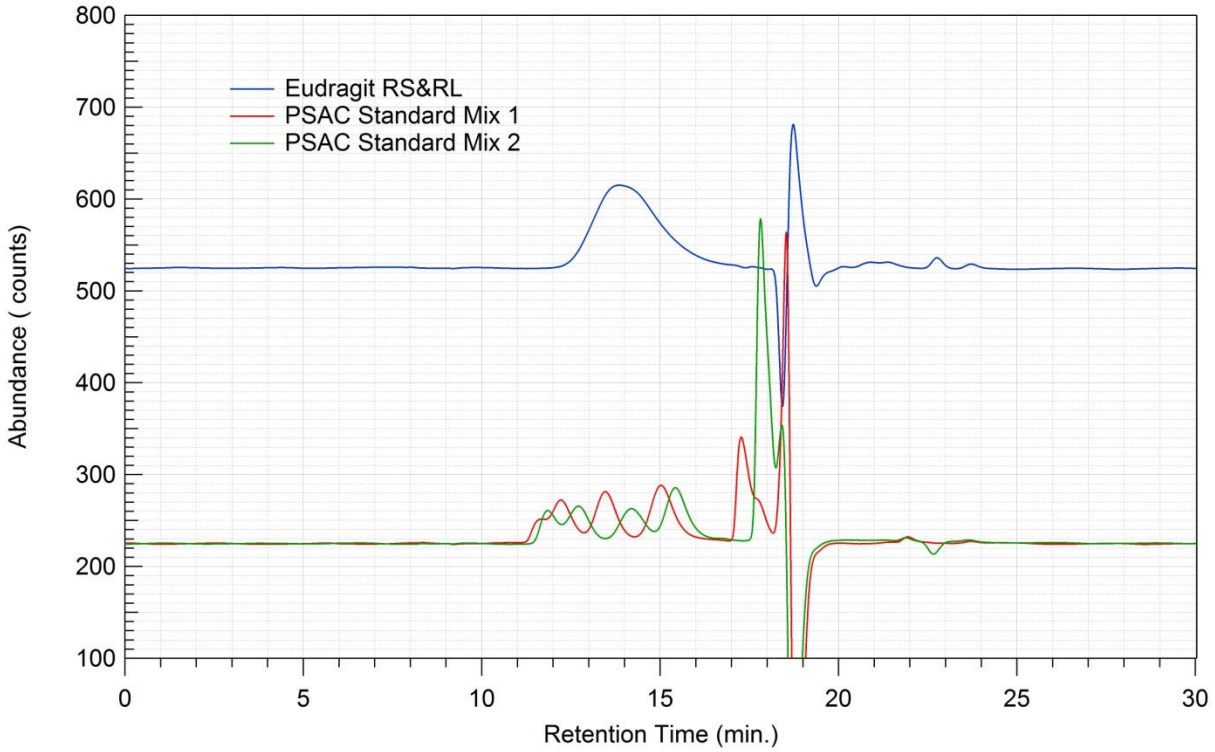

Figure 7. Refractive index (RI) chromatogram of Eudragit RS and RL (PSAC standard)

2. Ethylcellulose

Ethyl cellulose is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups. It is one of the non-toxic films and thickeners which are not water soluble.

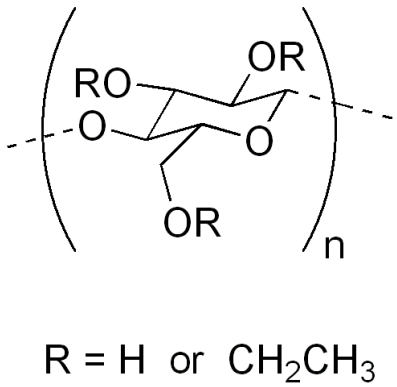

Figure 8. Chemical structure of ethylcellulose

Ethylcellulose is widely used in oral and topical pharmaceutical formulations including microencapsulation, sustained-release tablet coatings and tablet granulation. Similar to Eudragit, ethylcellulose coatings are also used to modify the release time of a drug, to mask an unpleasant taste, or to improve the stability of a formulation.

Sample Preparation

An ethylcellulose sample was dissolved into DMAc with 0.1M LiBr. 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 2**. The resulting weight fraction below 1 kDa is also presented in **Table 2**. The refractive index chromatogram is presented in **Figure 9**-**Figure 10**.

Table 2
Actual Mw Unknown

Polymer	M_n (Da)	M_w(Da)	M_z (Da)	PDI	Weight % < 1000 Da
Ethylcellulose (Relative to PS)	16,787	47,452	89,786	2.83	N.D.
Ethylcellulose (Relative to PSAC)	13,803	27,704	36,741	2.01	0.98

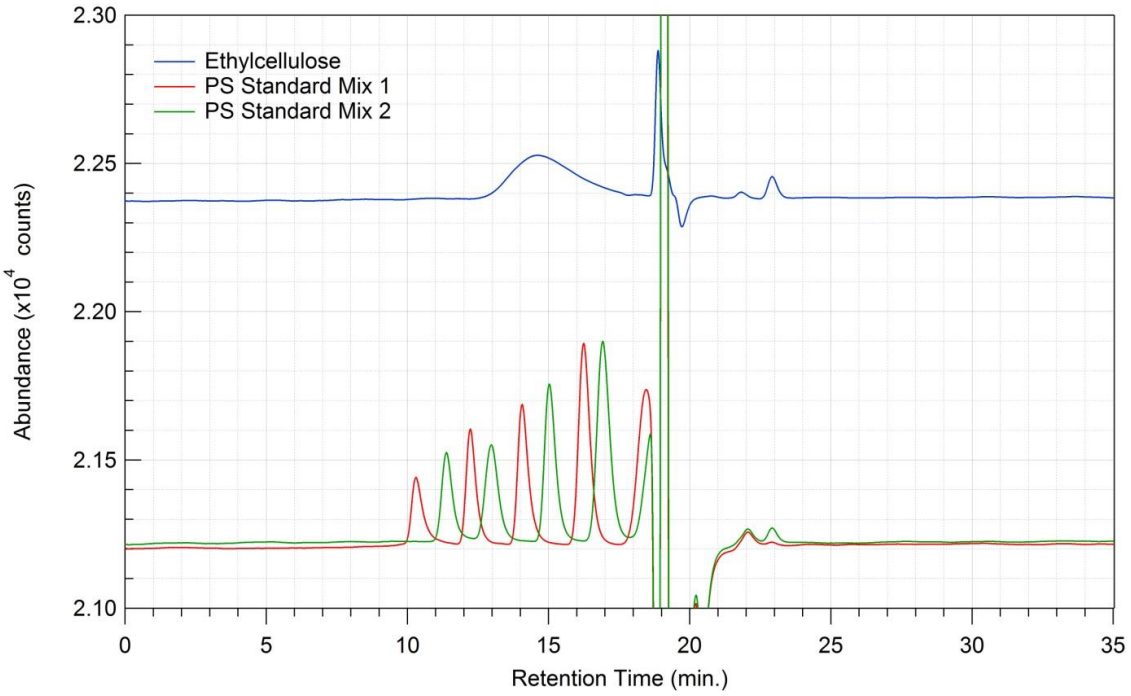

Figure 9. Refractive index (RI) chromatogram of ethylcellulose (PS Standards)

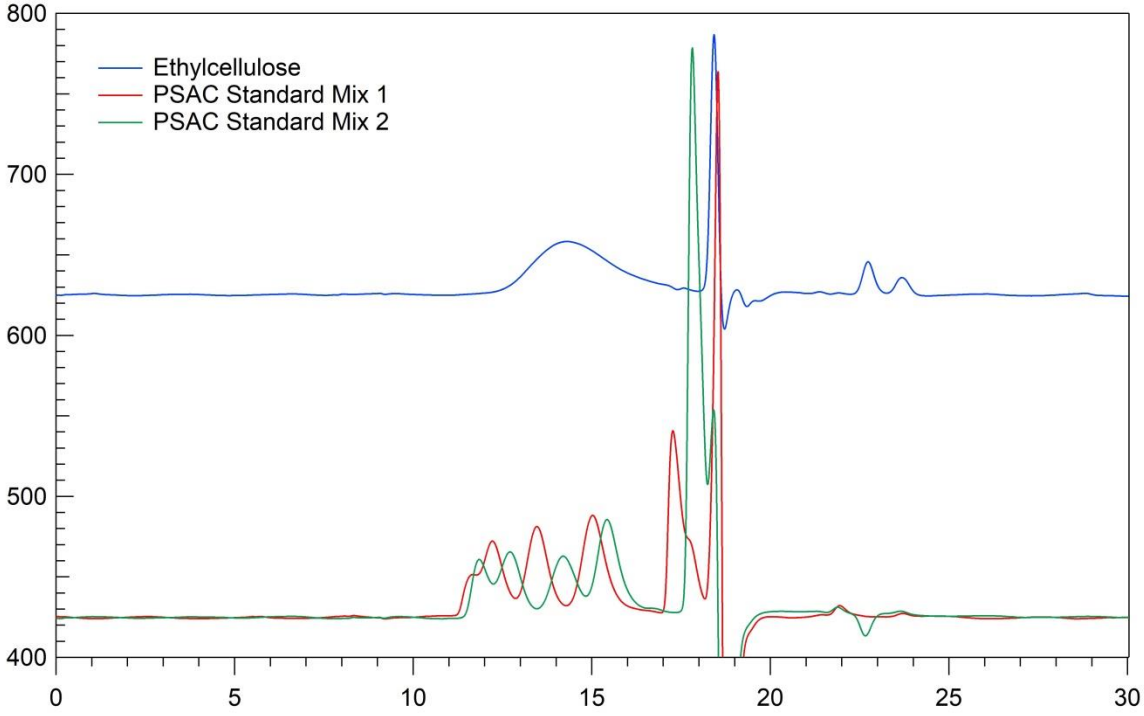

Figure 10. Refractive index (RI) chromatogram of ethylcellulose (PSAC Standards)

3. Cellulose Acetate

Cellulose acetate is the acetate ester of cellulose. Cellulose acetate is commercially prepared by treating cellulose with acetic acid and acetic anhydride in the presence of sulfuric acid.

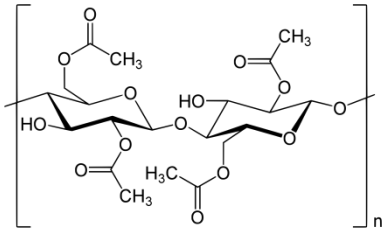

Figure 11. Chemical structure of cellulose acetate

Cellulose acetate possesses a series of properties beneficial to pharmaceutical drug delivery, including very low toxicity, endogenous and/or dietary decomposition products, stability, high water permeability, high T_g, film strength, compatibility with a wide range of medicinal ingredients, and ability to form micro- and nanoparticles.

Sample Preparation

A cellulose acetate sample was dissolved into DMAc with 0.1M LiBr 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 3**. The resulting weight fractions below 1 kDa is also presented in **Table 3**. The refractive index chromatogram is presented in **Figure 12-Figure 13**.

Table 3

Actual Mn Unknown

Polymer	M_n (Da)	M_w(Da)	M_z (Da)	PDI	Weight % < 1000 Da
Cellulose acetate (Relative to PS)	91,095	249,595	477,318	2.74	N.D.
Cellulose Acetate (Relative to PSAC)	54,974	140,031	1,122,811	2.55	N.D.

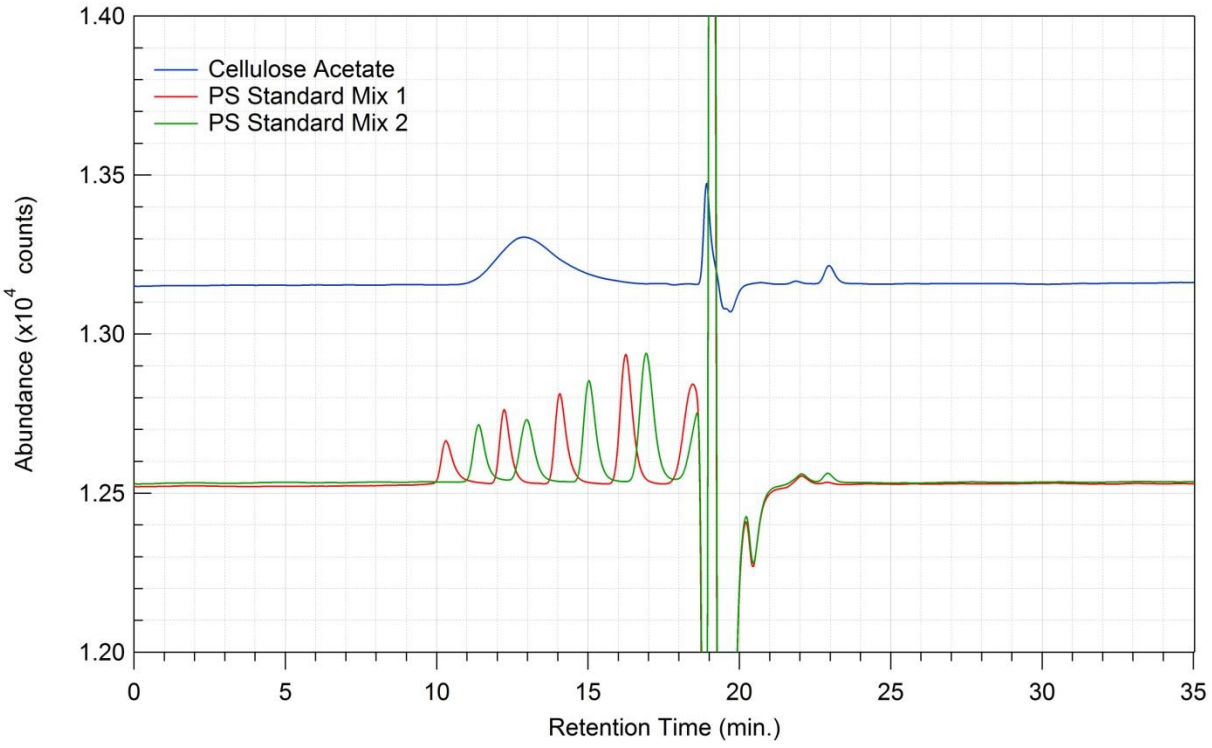

Figure 12. Refractive index (RI) chromatogram of cellulose acetate (PS Standards)

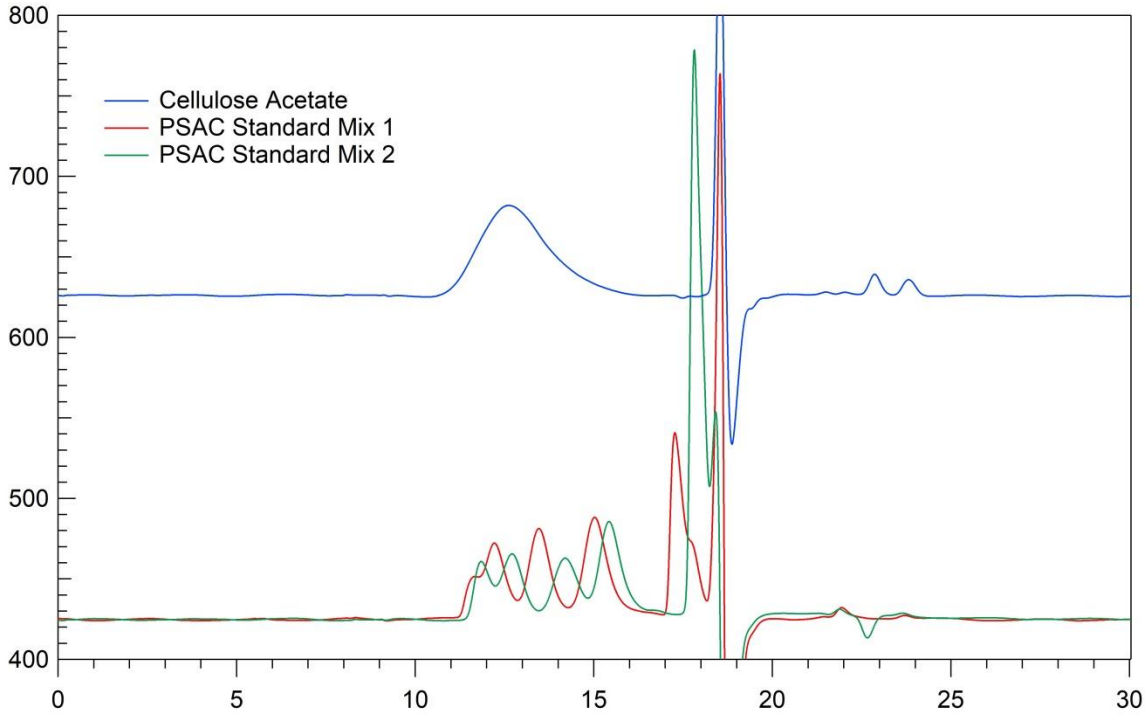

Figure 13. Refractive index (RI) chromatogram of cellulose acetate (PSAC Standards)

4. PAMAM Dendrimer

Dendrimers are the emerging polymeric architectures that are known for their defined structures, versatility in drug delivery and high functionality whose properties resemble biomolecules. **Poly(amidoamine) (PAMAM)** is made of repeated branched subunits of amide and amine functional groups and is one of the earliest and most widely studied dendrimers.

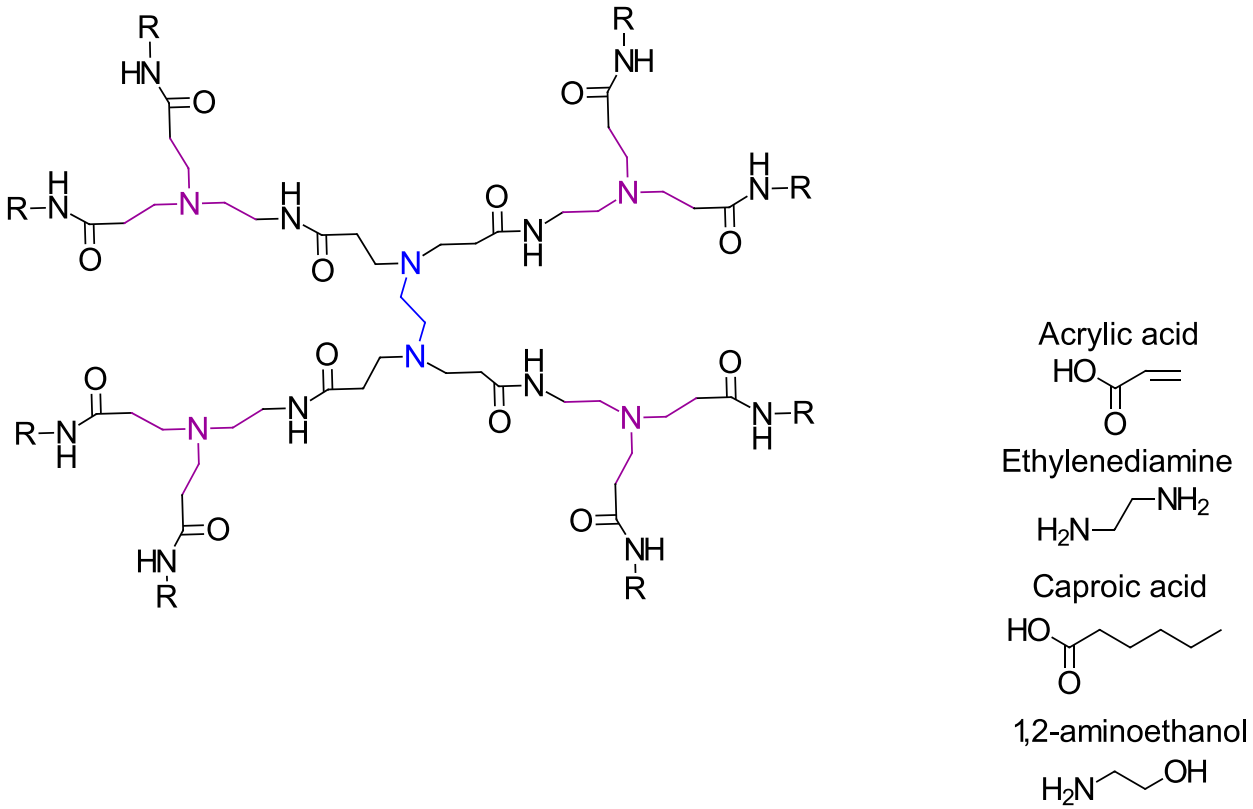

Figure 14. Chemical structure of PAMAM

These nanostructured macromolecules have shown their potential abilities in entrapping and/or conjugating the high molecular weight hydrophilic/hydrophobic entities by host-guest interactions and covalent bonding, respectively high ratio of surface groups to molecular volume has made them a promising synthetic vector for gene delivery.

Sample Preparation

A PAMAM dendrimer sample was dissolved into water with 0.1 M acetic acid and 0.01 M $NaNO_3$. 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 15**.

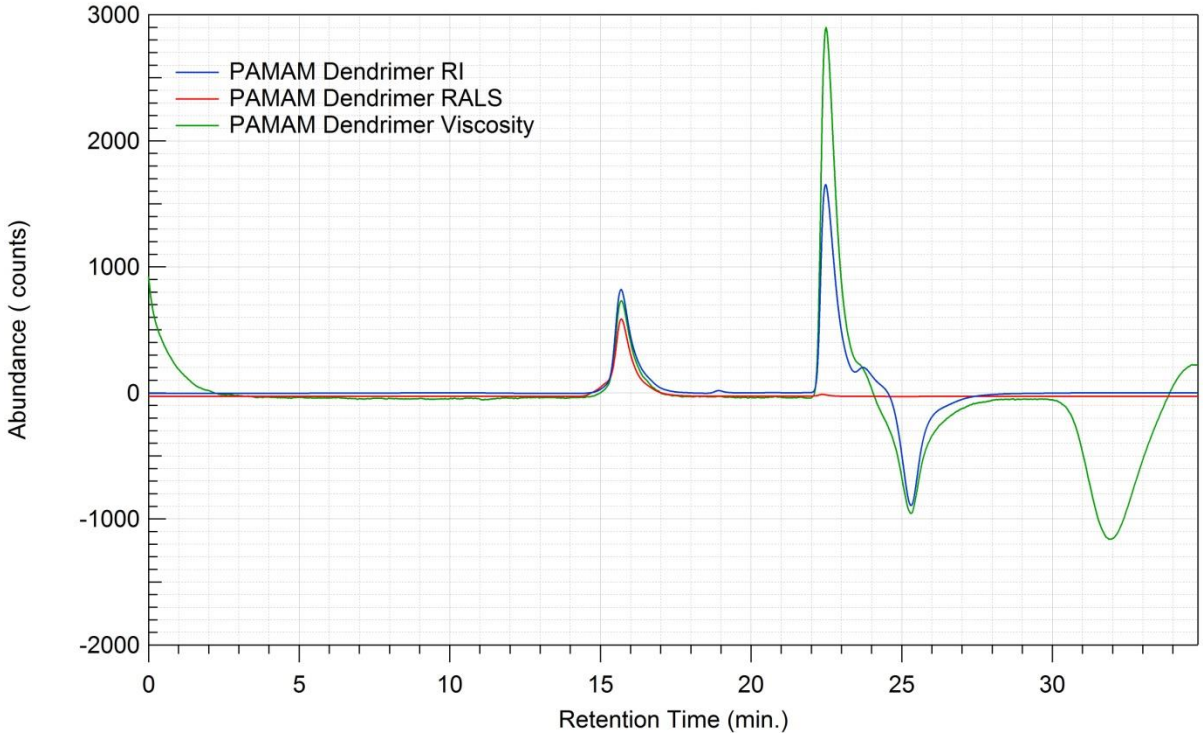

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Table 4

Actual Mw 14,000 Da

Polymer	M_n (Da)	M_w (Da)	M_z (Da)	PDI	Weight % < 1000 Da
PAMAM (Relative to PS)	4,766	7,288	9,162	1.53	2.29
PAMAM (GPC-T)	14,349	15,124	17,523	1.054	N.D.

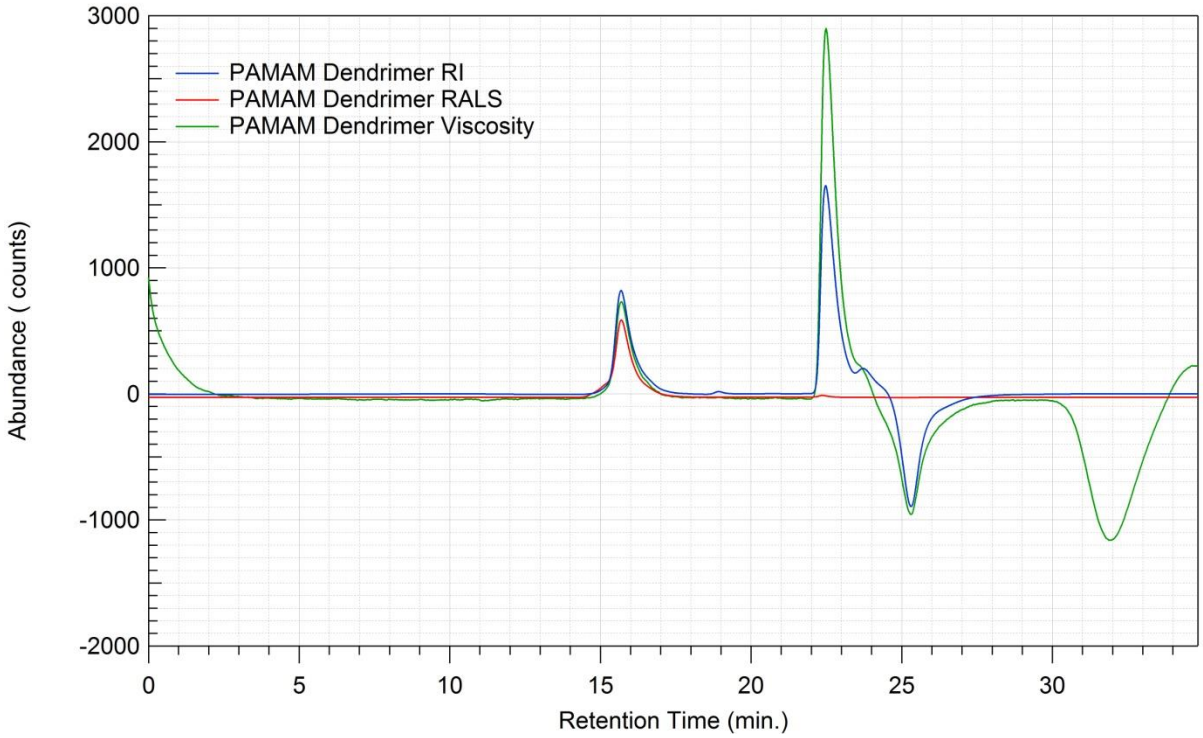

Figure 15. Refractive index (RI) chromatogram of PAMAM

5. Poly(D,L-lactide-co-glycolide) (PLGA)

Poly(D,L-lactide-*co*-glycolide (PLGA), a biodegradable and bioactive polyester, consists of alternating lactic acid and glycolic acid building blocks (**Error! Reference source not found.**). Low molecular weight PLGA is obtained through a direct condensation polymerization reaction of lactic acid and glycolic acid, while high molecular weight PLGA is produced via the ring opening polymerization of lactide and glycolide, the cyclic dimers of lactic acid and glycolic acid.

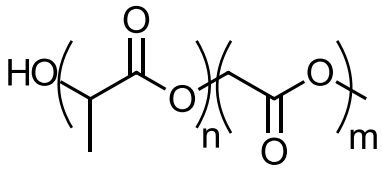

Figure 16. Chemical structure of PLGA

The properties of PLGA materials can be readily tuned by copolymerizing lactic acid and glycolic acid with varied monomer ratios. For example, a PLGA copolymer with a 1:1 monomer ratio incorporation degrades much faster than the individual homopolymers.

PLGA is unstable under physiological conditions and degrades into non-toxic products including lactic acid, glycolic acid, carbon dioxide, and water. PLGA is, therefore, used in several medical applications as its degradation products are found in various metabolic pathways of the human body and can be safely reabsorbed and processed. Specifically, PLGA is used in the fabrication of medical devices such as grafts, sutures, surgical sealant films, implants, prosthetic devices, and many more.[1]

Sample Preparation

A PLGA 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 17**.

[1] Y.H. Hsu, D.W.C. Chen, C.D. Tai, S.J. Liu*, E.C. Chan, ***International Journal of Nanomedicine***, 9, 4347-4355 (2014)

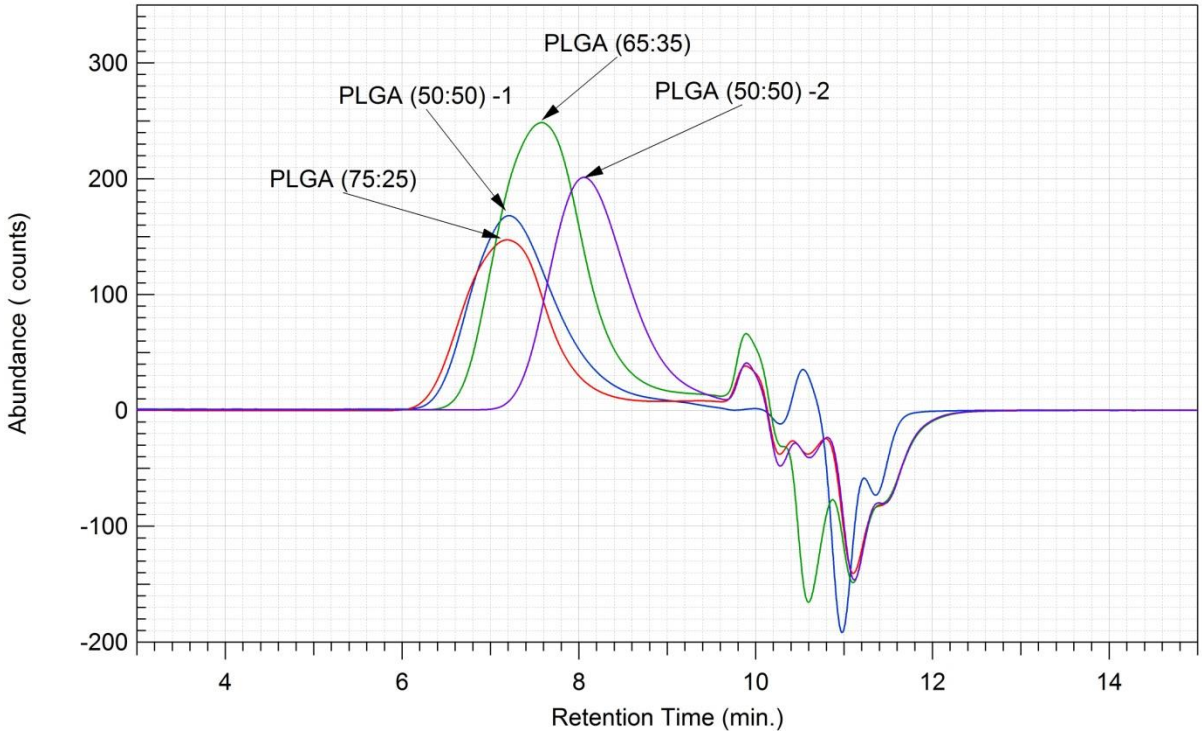

Figure 17. Refractive index (RI) chromatogram of PLGA

Table 5

Polymer	M_n (Da)	M_w (Da)	M_z (Da)	PDI	Weight % < 1000 Da
PLGA (50:50) -1 Relative to PS	11,344	28,098	44,660	2.48	1.02
PLGA (50:50)-1 Absolute	11,764	24,700	38,945	2.10	0.40
PLGA (50:50) -2 Absolute	6,864	12,131	18,739	1.77	0.40
PLGA (65:35) Absolute	19,567	34,970	54,221	1.79	N.D.
PLGA (75:25) Absolute	39,004	69,278	109,498	1.78	N.D.

Closing Comments

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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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