Analyzing Pharmaceutical Tablet and Capsule Excipients by Gel Permeation Chromatography (GPC) using Phenogel™ Columns

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Gel Permeation Chromatography (GPC) is used to separate and characterize polymers based on their size in solution which is directly related to their molecular weight and degree of polymerization (Dp). GPC separations are run using organic solvents (e.g. THF) and a combination of columns optimized to the molecular weight range being separated. In this study, several different organic polymers from tablets and capsules were analyzed by GPC using Phenogel columns to demonstrate its utility in characterizing excipients. Several classes of excipients such as binders, coatings, and suspending agents were run on Phenogel individual fixed pore size or mixed bed columns to show how certain tablets and capsules compare with standards. Phenogel columns were shown to be an excellent solution for the GPC of excipients.

Introduction

The active pharmaceutical ingredient (API) contained within a tablet or capsule is only a part of the effectiveness of a tablet formulation. The excipients contained within a tablet can have significant impact on the pharmacokinetics of a drug as well as a tablet's stability. As many of the excipients used in tablets and capsules are organic polymers that are somewhat polydisperse, traditional reversed phase chromatography is ineffective at characterizing a tablet formulation. Instead, much of the characterization and quality control of excipients in a tablet or capsule is based on analyzing the average molecular weight of the polymers used by GPC. Determination of average molecular weight, as well as the degree of dispersity, can inform formulation chemists in making decisions on optimizing the dissolution dynamics of a tablet or capsule.

While instrument parameters are seemingly simple with GPC because it is an isocratic method, there are two factors that are critical in developing a separation method: column selection and mobile phase. In general, methods are either developed using a series of molecular weight range columns (fixed pore size columns) or a series of similar mixed bed columns. Methods are balanced between run time and resolution; increasing the series of columns gives more resolution but with longer run times. Column selection is based on the molecular weight range of the polymer being analyzed. For widely dispersed polymers, a mixed bed column like the Phenogel Linear(2) can be used to give some resolution across a very wide molecular weight range. For increased resolution across a narrow molecular weight range, a fixed pore column provides a better solution. Often a combination of fixed pore sized columns can be used to widen the molecular weight range being analyzed.[1]

Mobile phase used can have an influence both with the separation as well as the analyte solubility. While many polymers will often separate well in THF, solubility of the polymer in THF may be incomplete and require a different solvent. In addition, viscosity of the diluent should be as close as possible to the mobile phase or "viscous fingering" can occur which can negatively impact peak efficiency and resolution. In this technical note, several examples of using GPC with Phenogel columns are shown to demonstrate its utility in analyzing different classes of excipients.[2]

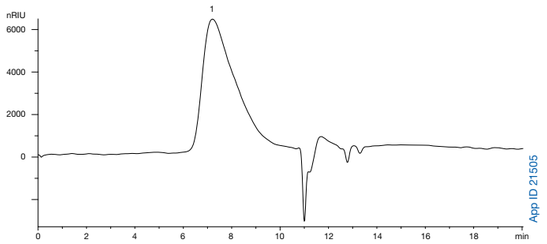
Materials and Methods

Excipient standards were purchased from Sigma Chemical (St. Louis MO, USA), solvents were purchased from EMD (San Diego, CA, USA), and tablet/capsule samples were purchased from a local drug store. Unless otherwise indicated, all standards and samples were dissolved in mobile phase before injection on GPC system. GPC separations were performed on an Agilent® 1260 HPLC system with autosampler, RI detector, and using ChemStation™ software (Palo Alto, CA, USA). All HPLC runs were isocratic at 1 mL/min and 40 °C unless otherwise stated. Mobile phase and the different Phenogel columns (all 300 x 7.8 mm) obtained from Phenomenex (Torrance, CA, USA) are listed in figure legends.

Results and Discussion

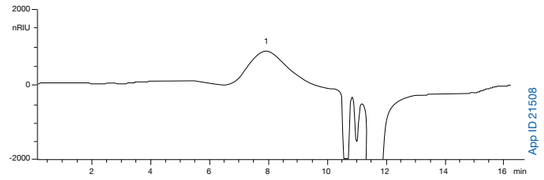
A common surprise for those new to performing GPC on polymers after using other separation methods is the broad peak shape and sometimes lack of multiple peaks in a run that is typical in small molecule analysis. Because the polymers used in many excipients are so disperse, they typically appear as one peak in a GPC run. **Figure 1** and **Figure 2** are typical examples of such behavior when analyzing common excipients. Polyvinylpyrrolidone (PVP or povidone) is commonly used as a tablet binder. In **Figure 1**, a polyvinylpyrrolidone standard was injected on a pair of Phenogel Linear(2) columns running at 2 mL/min in DMF (with 10 mM LiBr). As one can see, the polymer injected presents a very broad molecular weight distribution demonstrating the value of using a mixed bed linear phase for those types of samples.

Figure 1.
Separation of polyvinylpyrrolidone (povidone) on 2x Phenogel Linear(2) column using DMF as mobile phase. Povidone is a common binder and filler agent used in tablet formulations. Note the wide MW distribution on a GPC column.



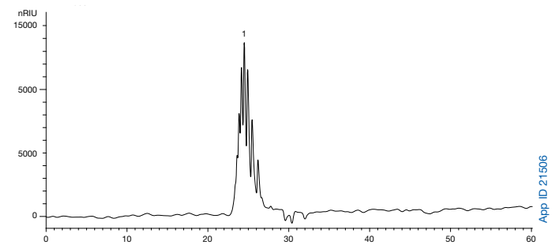
An even more extreme case is shown in **Figure 2** where a cellulose acetate sample was injected on the same pair of Phenogel Linear(2) columns. In this example, cellulose acetate was even more disperse making determination of a mean molecular weight somewhat difficult. The mixed bed Phenogel Linear(2) phase is designed to separate across a wide range of molecular weights and is ideal for wide distribution polymers as well as general all-purpose screening for GPC separations.

Figure 2.
GPC separation of cellulose acetate using 2x Phenogel Linear(2) columns. Cellulose acetate is also used as a binder for tablets and is very polydisperse leading to a very broad peak. Mixed bed linear phases are well suited for wide MW distribution separations.



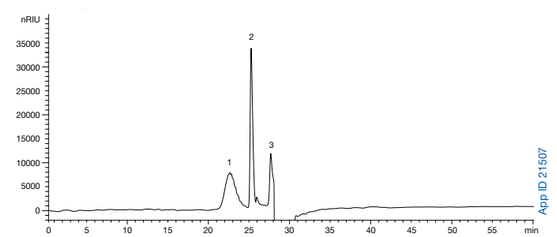
For improved resolution across a narrow molecular weight, a fixed pore size column is designated. Such columns can be used in series or combined with other fixed pore size columns to get a slightly wider molecular weight range for a separation. Good examples of this are shown in **Figure 3** and **Figure 4** where polyethylene glycol (PEG), a common tablet binder and solubilizing agent in liquid formulations was analyzed. In these examples, a series of 50 Å, 100 Å, and 500 Å Phenogel fixed pore size columns were combined and run using THF at 1 mL/min. **Figure 3** is the GPC chromatogram of a PEG standard mixture on these three Phenogel columns in series. In the case of the PEG standard, there is enough resolution between specific polymer lengths to potentially quantitate specific PEG species in the mixture. This can be very useful when analyzing a specific formulation as is shown in **Figure 4**.

Figure 3.
GPC separation of a polyethylene glycol (PEG) standard using 3 fixed pore size Phenogel columns (50 Å, 100 Å, and 500 Å) and THF mobile phase at 1 mL/min. Fixed pore size columns can provide increased resolution of narrower MW ranges compared to the mixed bed linear phases. Note that discrete MW species can be resolved.



In **Figure 4**, Advil® Cold & Sinus Liquid-gels® were dissolved in THF and injected on the same series of three Phenogel columns. Closer inspection of the chromatogram reveals a specific peak for PEG as well as a diffuse early eluting peak and peak corresponding to the API in the mixture that elutes close to the void volume peak. This example shows how GPC separation using Phenogel fixed pore size columns can potentially separate and quantitate multiple components in an excipient mixture.

Figure 4.
GPC separation of an Advil® Cold & Sinus Liqui-gels® sample. Note the corresponding peaks to API as peak 3, PEG as peak 2, and a larger disperse polymer (i.e. gelatin) as peak 1. The combination of the 3 fixed pore size Phenogel columns (50 Å, 100 Å, and 500 Å) in series can give a slightly wider range than one specific fixed pore size column.



Conclusion

While often overlooked in the past, characterization and quality control analysis of excipients in a tablet, capsule, and even syrup has been of increasing importance in the pharmacokinetics, customer usability, as well as detection of fraudulence in pharmaceutical drugs. Since many of the components in a tablet or capsule formulation are polymers, analyzing by reversed phase chromatography does not always provide useful data for determining the composition or physical characteristics of the drug.

Performing GPC using Phenogel columns provides solutions for analyzing and quantitating excipients in tablet or capsule formulation that other analytical methods cannot. The key to obtaining useful data for excipient analysis is understanding the method development parameters of GPC chromatography which include column phase and mobile phase selection. Such parameters are often unique to the physical characteristics of a specific type of polymer which include size and solvent solubility. Such input impacts the development of a rugged and accurate GPC method.

References

1. A User's Guide to Gel Permeation Chromatography: Phenomenex Publication, July 2000 www.phenomenex.com
2. B. S. Broyles, R.A. Shalliker, D.E. Cherrak, and G. Guiochon; *Journal of Chromatography A*: V822 (2) Pg 173-187 (1998).

APPLICATIONS

Phenogel™ Ordering Information

5 µm Columns (mm)		300 x 7.8	Guards 50 x 7.8
Pore Size	**MW Range**		
50 Å	100-3 K	00H-0441-K0	03B-2088-K0
100 Å	500-6 K	00H-0442-K0	03B-2088-K0
500 Å	1 K-15 K	00H-0443-K0	03B-2088-K0
10^3 Å	1 K-75 K	00H-0444-K0	03B-2088-K0
10^4 Å	5 K-500 K	00H-0445-K0	03B-2088-K0
10^5 Å	10 K-1,000 K	00H-0446-K0	03B-2088-K0
10^6 Å	60 K-10,000 K	00H-0447-K0	03B-2088-K0
		300 x 7.8	**50 x 7.8**
Mixed Beds			
Linear(2)	100-10,000 K	00H-3259-K0	03B-2088-K0

5 µm Narrow Bore (NB) Columns (mm)		300 x 4.6	Guards 30 x 4.6
Pore Size	**MW Range**		
50 Å	100-3 K	00H-0441-E0	03A-2088-E0
100 Å	500-6 K	00H-0442-E0	03A-2088-E0
500 Å	1 K-15 K	00H-0443-E0	03A-2088-E0
10^3 Å	1 K-75 K	00H-0444-E0	03A-2088-E0
10^4 Å	5 K-500 K	00H-0445-E0	03A-2088-E0
		300 x 4.6	**30 x 4.6**
Mixed Beds			
Linear(2)	100-10,000 K	00H-3259-E0	03A-2088-E0

10 µm Columns (mm)		300 x 7.8	Guards 50 x 7.8
Pore Size	**MW Range**		
50 Å	100-3 K	00H-0641-K0	03B-2090-K0
100 Å	500-6 K	00H-0642-K0	03B-2090-K0
500 Å	1 K-15 K	00H-0643-K0	03B-2090-K0
10^3 Å	1 K-75 K	00H-0644-K0	03B-2090-K0
10^4 Å	5 K-500 K	00H-0645-K0	03B-2090-K0
10^5 Å	10 K-1,000 K	00H-0646-K0	03B-2090-K0
10^6 Å	60 K-10,000 K	00H-0647-K0	03B-2090-K0
		300 x 7.8	**50 x 7.8**
Mixed Beds			
Linear(2)	100-10,000 K	00H-3260-K0	03B-2090-K0

Other Shipping Solvents: Methanol, Methylene Chloride, Cyclohexane, Ethyl Acetate, NMP, DMAC, DMF	
Size (mm)	**Price**
30 x 4.6	
50 x 7.8	
300 x 4.6	
300 x 7.8	

NOTE: Phenogel columns are routinely shipped in THF. Columns can be shipped in Toluene and Chloroform upon request at no additional charge.

guarantee

If Phenomenex products in this technical note do not provide at least an equivalent separation as compared to other products of the same phase and dimensions, return the product with comparative data within 45 days for a FULL REFUND.

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