Melt Extrusion Failure of Ethylene Vinyl Acetate Excipients Assessed by Gel Permeation Chromatography

Application Note

Pharmaceuticals

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There are many methods for producing three-dimensional structures that allow the controlled or sustained release of pharmaceutically active compounds within the body. Most revolve around formulation of the active pharmaceutical ingredient (API) with a polymer excipient that can be shaped to complement the implantation point and give the desired release profile.

One such technique is hot melt extrusion. In this method, an active pharmaceutical ingredient is mixed in solid form with a suitable polymeric excipient and passed through a melt extruder, where the polymer and API are simultaneously melted, mixed, and then extruded in a string or rod form. The material may then be repelletised or molded into the desired final shape. Advantages of this approach are the simple and continuous manufacturing conditions and the ability to process moisture sensitive drugs without solvents.

The hot melt extrusion process requires a nontoxic, bio-inert polymer with a relatively low melting point, such that the temperatures required for the extrusion process do not damage the API. One such material is ethylene vinyl acetate (EVA). The presence of the vinyl acetate groups break up the normal highly crystalline structure of polyethylene, resulting in a lower melting point and amorphous domains through which the API can diffuse and be released.

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Extrusion issues

This application note describes the investigation into three grades of EVA to be used for controlled release of an API after hot melt extrusion. The three grades were manufactured to different target molecular weights and, therefore, were known to require different melt temperatures during the extrusion process. However, it was found that one of the materials did not extrude as expected and caused issues with the hot melt extruder. These three samples were investigated to see if the physical cause of the problem could be ascertained.

Materials and Methods

Liquid chromatography was used to investigate the properties of the three grades of EVA. As EVA is a polymer, the analytical technique of choice is gel permeation chromatography (GPC). This technique allows determination of the molecular weight distribution of polymers, a property that controls many of their physical properties. The GPC mechanism works by introducing the dissolved sample into liquid flowing through a column packed with spherical porous particles of controlled pore and particle size. Separation occurs through the partitioning of coiled polymer molecules between the mobile liquid phase and static liquid trapped in the pores of the column. Smaller polymer coils have access to a larger number of pores than larger molecules (assuming the correct pore size column is chosen) and, thus, take longer to elute from the column. The result is a separation based on the size and, therefore, molecular weight of the polymer molecules.

GPC analysis of EVA requires high temperatures because the high crystallinity of the ethylene component of the polymer will only dissolve above approximately 120 °C; below this temperature, the material precipitates from solution. Therefore, the analysis was performed on an Agilent PL-GPC 220 High-Temperature GPC system in trichlorobenzene, a good solvent for ethylene vinyl acetate. The analysis was performed with three Agilent PLgel 10 µm MIXED-B, 7.5 × 300 mm columns, connected in series to improve resolution.

Conditions

Columns:	3 x Agilent PLgel 10 µm MIXED-B, 7.5 × 300 mm (p/n PL1110-6100)
Sample:	Ethylene vinyl acetate
Eluent:	Trichlorobenzene + 0.0125% BHT
Injection volume:	200 µL
Flow rate:	1.0 mL/min
Temperature:	160 °C
Detector:	Differential refractive index
System:	Agilent PL-GPC 220 High Temperature GPC

Results and Discussion

Figure 1 shows chromatograms for the three samples of EVA.

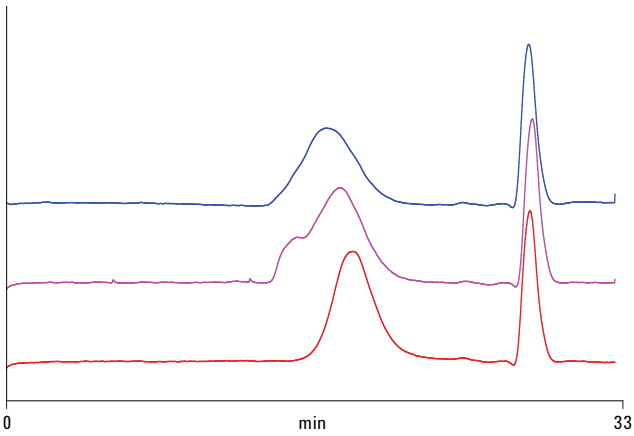

Figure 1. Overlaid chromatograms of the three EVA samples; A (blue), B (purple), and C (red).

Earlier elution of the peak maximums indicates a higher peak molecular weight. As was expected for these samples, the peak molecular weight decreases for samples A through to C. However, it is also apparent that the middle sample has a different peak profile than the other two samples. Sample B has a conspicuous early eluting shoulder, whereas samples A and C are near Gaussian in peak shape.

Using the chromatograms and a polystyrene calibration curve generated from polystyrene standards, molecular weight distributions were generated for the three samples and overlaid using the Agilent GPC/SEC software, as shown in Figure 2.

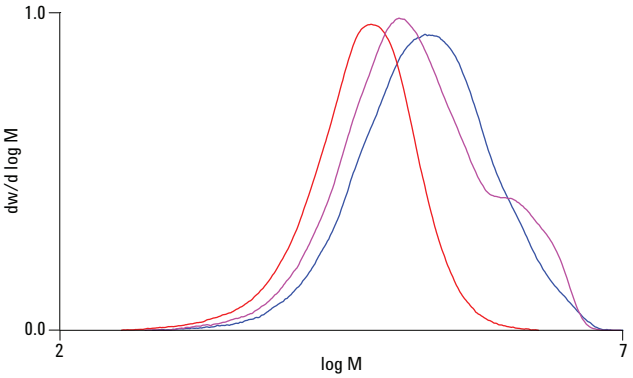

Figure 2. Overlaid molecular weight distributions for three samples of ethylene vinyl acetate; A (blue), B (purple), and C (red)

The molecular weight distributions clearly show the increasing molecular weight of the samples, as illustrated by the peaks moving from the left to the right. However, the peak shape of sample B is clearly different, showing a large shoulder at high molecular weight that is not seen on the profiles of the other two peaks. Sample B has a higher content of high molecular weight material than samples A and C, and it was this sample that had not been behaving as expected in the melt extrusion process.

Conclusions

It is well-known that molecular weight affects the melt flow properties of polymers. The presence of high molecular weight material can cause a significant increase in melt viscosity that can affect flow through an extruder. In this case, the presence of high molecular weight material in EVA sample B was the cause of the unusual flow behavior and issues with extrusion. For this reason, sample B was returned to the manufacturer as being unsuitable for use.

For More Information

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