APPLICATION NOTE 031

New GPC-IR Analysis of Polymeric Excipients in Pharmaceutical Formulations

The DiscovIR-LC is a powerful new tool for materials analysis. When connected to the outlet of a LC column, the DiscovIR deposits LC eluants as a continuous track on an infrared transparent substrate. The built-in interferometer simultaneously captures a set of time-ordered infrared spectra from the deposited track. Sample data collection and data processing are executed by GRAMS AI™ software resident on the DiscovIR system.

When analyzing polymers the chromatographic eluant deposits as a continuous track of sample, ranging from high molecular weight to low. This resultant map of molecular structure of all regions of a polymer GPC separation enables characterization of the distribution of the sample comonomers.

SUMMARY

This application note describes the characterization of a copolymer frequently used as an excipient in pharmaceutical formulation. The copolymer polyvinyl pyrrolidone/vinyl acetate (PVP/VAc) was analyzed by the hyphenated method of Gel Permeation Chromatography (GPC) – Fourier Transform Infrared spectroscopy (FTIR). The sample examined demonstrated a significant composition drift (changes of the relative concentration of the comonomers) across the elution profile (molecular weight distribution). The variability of excipient composition affects hydrophilicity, dissolution behavior, and possibly the kinetics of drug release.

INTRODUCTION

Polymeric excipients serve various functions in pharmaceutical products. Some of the major functions they provide are listed in the table below.

<table>
<thead>
<tr>
<th>Function</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet binding agent</td>
<td>Film former (povidone-iodine)</td>
</tr>
<tr>
<td>Granulation agent</td>
<td>Suspension stabilizer</td>
</tr>
<tr>
<td>Sustained release agent</td>
<td>Stabilize labile chemicals</td>
</tr>
<tr>
<td>Plasma expander</td>
<td>Crystallization inhibitor</td>
</tr>
<tr>
<td>Lyophilization agent</td>
<td>Matrix former for melt-extrusion tablets</td>
</tr>
<tr>
<td>Modulate release of active ingredients</td>
<td>Enhance solubilization, drug release and bioavailability</td>
</tr>
</tbody>
</table>
An important excipients application is the controlled release of Active Pharmaceutical Ingredients (API). This application embraces oral, parenteral, and topical dosage forms. By forming a nanoscale dispersion of an API with appropriate excipients, it is possible to modulate the release profile of an API.

An example of this is the use of a copolymer of polyvinyl pyrrolidone and polyvinyl acetate (Copovidone) and an API to produce controlled release forms of various drugs. The drug and copolymer are combined in a melt-extrusion process, the result being a solid ingestible tablet possessing controlled release characteristics. This polymer serves as a dispersant and solubilization enhancer for various APIs. “Pyrrolidone rings can form hydrogen bondings that facilitate the dissolution or interaction of sparingly soluble active ingredients. The polymeric matrix disperses the drug and uniformly enhances its bioavailability by preventing the API from recrystallizing when in contact with the gastrointestinal fluid.” Release properties are modulated by the presence of the less hydrophilic vinyl acetate comonomer.

Fig. 1. Chemical structure of PVP/PVAc

\[(\text{C}_\text{H}_\text{N}_\text{O})_n, (\text{C}_\text{H}_\text{O})_m\]

\[M_r (111.1)_n + (86.1)_m\]

The PVP/VAc used is a random linear copolymer synthesized from n-vinyl-2-pyrrolidone and vinyl acetate in a mass ratio of 6:4. Compared to the PVP homopolymer, the copolymer PVP/VAc has a lower hydrophilicity, lower glass transition temperature, and more pliability. The comonomer ratio may also affect the solubility and biorelease characteristics of the resultant drug formulation.

Copolymers such as this provide the synthesis chemist with a great deal of latitude in adjusting various physical and chemical properties by control of the comonomer ratios. Their synthesis however involves process complexity over and above that of homopolymers. Copolymers intrinsically tend to composition heterogeneity (compositional drift) during synthesis. Any difference in the reaction rates of the comonomers shifts the incorporation amounts in the growing polymer chains. Various synthesis strategies are used to counteract this effect, including stepwise addition of comonomers, controlled continuous flow of monomers into the reactor, and the use of multiple catalysts/accelerants during polymerization. In many copolymer applications, comonomer composition variation must be limited to a few percent variation of composition across the molecular weight distribution.

In many applications it is desirable to minimize copolymer compositional drift. Elastomeric copolymers are frequently added to optically clear base polymers such as polystyrene to increase impact resistance. Compositional drift can reduce the compatibility of such formulations, resulting in haze in the end product. On the other hand the use of a copolymer with a tailored drift profile can prove superior in increasing the fracture energy of adhesive formulations.
Spectra Analysis has characterized Copovidone by the hyphenated technique of GPC-FTIR. In this hyphenated analysis the sample is run through a GPC to separate the polymer molecules on the basis of their molecular size, with the resulting eluant stream continuously examined by FTIR. The resultant data matrix is an ordered sequence of infrared spectra vs. molecular size.

Figure 2 presents the bulk IR spectra of the two homopolymers, polyvinyl pyrrolidone and polyvinyl acetate. Each of the two spectra exhibit some spectral bands not present in the other polymer. This provides a good basis for quantitative characterization of the copolymer composition. We have utilized the strong carbonyl bands of PVP (1680 cm⁻¹) and PVAc (1740 cm⁻¹) to measure the comonomer ratios of Copovidone as a function of molecular weight.

**EXPERIMENTAL**

The sample analyzed here was Copovidone (BASF Kollidon® VA64). The sample was injected onto a GPC column, and column eluant was directed to a DiscovIR-LC system.

<table>
<thead>
<tr>
<th>Column</th>
<th>Shodex OHpak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile phase</td>
<td>MeOH/H2O, 0.05M Acetic Acid</td>
</tr>
<tr>
<td>Flow rate</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>Injection volume</td>
<td>150 μl</td>
</tr>
<tr>
<td>Sample concentration</td>
<td>0.35%</td>
</tr>
</tbody>
</table>

Figure 3 displays the time ordered array of IR spectra. The x-axis depicts spectral wavenumbers, the z axis (vertical) shows spectral band intensities, and the y-axis depicts elution time (correlates to molecular weight). The carbonyl peaks generated by the comonomers are evident as a strong pair of bands in the middle of the spectral map.
When examining various samples of PVP/VAc we found that they exhibited compositional drift of the comonomer ratio. We also noted that samples from various sources showed varying compositional profiles. This implies that a polymer sample of stated and assayed bulk composition actually consists of an array of polymer molecules which vary in both comonomer composition and chain length. There was a consistent trend among these samples for the pyrrolidone content to be greatest in the high molecular weight eluant and to decrease with later eluting (lower molecular weight) fractions.

Figure 3 shows a three-dimensional view of the time-ordered set of infrared spectra obtained from the DiscovIR instrument. Figure 4 shows the mid-IR spectra of two samples from the data set at 8 and 10 minutes elution times. It is apparent that relative intensities of some spectral bands are different in these two snapshots of the composition map.
Figure 5 depicts an overall infrared (peaks) chromatogram of the experiment. The red superimposed line is a ratio chromatogram of the 1740 spectral band height divided by the 1680 band height. Such a ratio chromatogram reflects solely the comonomer composition, with the film thickness automatically cancelled from the function of absorbance ratios [see Appendix Formula (2)].

The bulk comonomer composition of Copovidone is a mass ratio of 4:6 (VAc/VP) comonomers. Figure 5 shows that the infrared band ratio of vinyl acetate to vinyl pyrrolidone increases markedly with increasing elution time (decreasing molecular weight).

The band ratio chromatogram was converted to a chromatogram of the acetate comonomer content vs. elution time (see Appendix section). This chromatogram is displayed in Figure 6.
Although the overall composition of the PVP/VAc copolymer is 40% acetate, it is apparent that the composition of the high molecular weight early elution fraction is <35% acetate (more hydrophilic), and rises to 45% acetate (less hydrophilic) in the low molecular weight region. The continuum of polymer composition exhibits a variation of about 36% (low to high acetate content) across the chromatogram.

DISCUSSION

Drug release profiles are often controlled by polymeric excipients. “By selecting the polymer or polymer combination, or by combining with other excipients (e.g. surfactants) a number of different active ingredient release profiles can be achieved.” Varying the type of polymer used can provide in-vivo drug delivery in a time range of less than a few minutes to more than 24 hours. The tailoring or release characteristics can be achieved either with excipient polymer blends, or with copolymers of controlled comonomer composition. Release kinetics could be quite sensitive to relatively small variation of homopolymer blend ratios.

As Figure 6 shows there is a wide range of comonomer composition demonstrated in the Kollidon VA64 sample analyzed. The comonomer content influences polymer binding capacity for an API, hydrophobicity, solubility upon ingestion, and release kinetics.

Copolymers intrinsically tend to composition heterogeneity from copolymerization process. Any difference in the reaction rates of the comonomers shifts the incorporation amounts in the growing polymer chains. Various synthesis strategies are used to counteract this effect, including stepwise addition of comonomers, or controlled flow of monomers into the reactor, and control factors which influence the kinetics of monomer reaction rates. In many copolymer applications, comonomer composition variation must be limited to a few percent variation of composition across the molecular weight distribution. Balanced against this, a precisely controlled and repeatable composition drift in a copolymer can be exploited to optimize the performance of a copolymer used for a specific application.

The compositional drift exhibited in the sample analyzed suggests that there will be a wide range of coincident API release rates. It also suggests that users of a Copovidone copolymer must be cognizant of compositional heterogeneity, and possible lot-to-lot variation. Copovidone and similar copolymers are available from a number of producers worldwide. Spectra Analysis has noted differences in compositional drift in different commercial samples we have examined. We tentatively conclude that the bulk content specification of acetyl content may be inadequate to define the binding and release characteristics of the polymer, and that compositional drift may a desired specification of acceptance criteria.

In the manufacture of controlled release pharmaceutical products, product consistency is a paramount requirement. The LC-FTIR technology embodied in the DiscovIR-LC provides a rapid, easy to use control tool for routine monitoring of drug formulations, while also providing insight to the excipient properties not readily apparent in traditional bulk assays.
Appendix

This spectral band ratio chromatogram can be transformed to a chromatogram of one of the comonomers concentration across the elution profile. The DiscovIR data analysis software enables the user to perform various mathematical transforms of infrared chromatograms.

The conversion rests on the assumption that each comonomer generates a spectral band that is not convolved with the other comonomer. As can be seen in Figure 4, both comonomers have strong carbonyl bands at 1740 cm\(^{-1}\) (Vinyl acetate) and 1680 cm\(^{-1}\) (Vinyl pyrrolidone).

\[
A_{v,i} = \varepsilon_v b C_i
\]

\(A_{v,i} = \text{absorbance of component } i \text{ at wavenumber } v\)
\(\varepsilon_v = \text{molar absorptivity of component } i\)
\(b = \text{film thickness}\)
\(C_i = \text{fraction of component } i \text{ in the FTIR sample beam}\)

Equation (2) defines the band ratio chromatogram in terms of the concentrations of the comonomers. Note that the deposited film thickness (overall mass) cancels out. The band ratio chromatogram reflects only the relative concentrations of the comonomers.

\[
\frac{A_{vA,i}}{A_{vP,i}} = k \frac{b C_{vA,i}}{b C_{vP,i}} = k \frac{C_{vA,i}}{C_{vP,i}}
\]

\(\frac{A_{vA,i}}{A_{vP,i}} = \text{ratio of Acetate/Pyrrolidone chromatograms}\)
\(k = \frac{\varepsilon_{vA,i}}{\varepsilon_{vP,i}} = \text{ratio of extinction coefficients}\)

The extinction coefficients of the comonomers are not per se known, and cannot be assumed to be the same as those of the individual monomers. If the bulk concentration of the two comonomers is known, the following technique can be used to generate an extinction coefficient ratio. Equation (3) integrates (sums) the data set absorbance values across the elution profile, and relates this to the known bulk composition.

\[
\frac{\sum_{j=1}^{N} A_{vA,i}}{\sum_{j=1}^{N} A_{vP,i}} = k \cdot \frac{0.4}{0.6}
\]

0.4, 0.6 are the bulk concentrations of the comonomers
The band ratio chromatogram can now be in terms of the solved value for $k$ and comonomer ratio.

\[
\frac{A_{\nu A}}{A_{\nu P}} = k \frac{C_{\nu A}}{C_{\nu P}} = k \frac{C_{\nu A}}{1 - C_{\nu A}}
\]  

(4)

(5) To simplify conversion of the bands ratio chromatogram, let

\[
q_t = \frac{1}{k} \frac{A_{\nu A}}{A_{\nu P}}
\]

Algebraic substitution yields

\[
C_{\nu A} = \frac{q_t}{(1 + q_t)} \times 100
\]  

(6)

Figure 7 shows the 1680 cm\(^{-1}\) band chromatogram and its integral. The scalar value of the integral at 12 minutes was 0.49184. The value of the 1740 cm\(^{-1}\) band chromatogram integral was similarly determined to be 0.31002. The numeric value of $k$ in equation (3) is therefore is 0.94549.

Using equations (5) and (6), the band ratio chromatogram was transformed into the $q_t$ chromatogram, and then into the form of equation (6). This defines the changing concentration of the vinyl acetate comonomer across the elution profile.