Variability Of Polymeric Excipients And Its Effect On Drug Delivery Performance

Polymer excipients are increasingly used to enhance and control the delivery of APIs. They play an especially crucial role in delivery of poorly soluble drugs.
An oral drug must:

- Withstand the rigors of the compounding and fabrication processes
- Retain efficacy during shelf life
- Make the passage through the stomach without undue decomposition
- Be released in the GI tract with adequate bioavailability and with a desired release kinetic profile.

Performance is achieved by control of both the chemical and physical properties of the excipient package. Both polymer blends and copolymers are used in this field. A copolymer offers opportunity to fine-tune various attributes of the polymer. Copolymers avoid the issue of immiscibility of blended homopolymers. In some applications block copolymers, rather than random copolymers are used to obtain precise sharp release characteristics.
A polymer is not a chemical compound per se, but rather a population of similar molecules that simultaneously vary in a number of physical and chemical properties (chain length, composition, configuration, stereoregularity, conformation). These properties will determine the performance properties (solubility, diffusivity, API binding affinity, hygroscopicity, etc.) of the excipient API package.

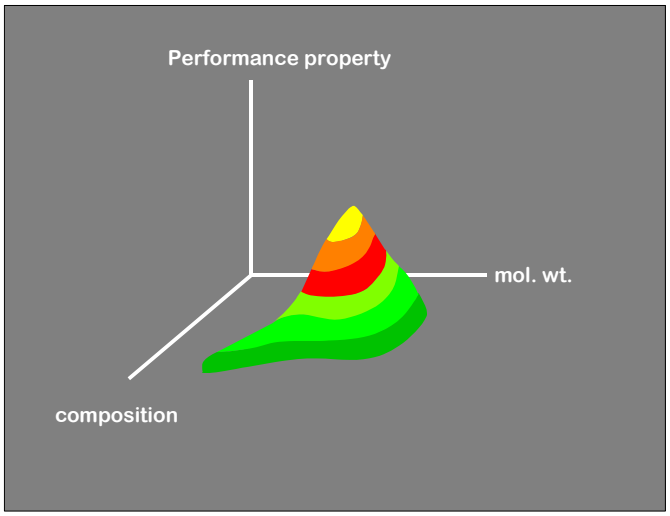


Figure 1 Conceptual properties and performance N-space of excipient polymers

Copovidone is one of a family of polymeric excipients. It is a random linear copolymer of vinyl pyrrolidone and vinyl acetate comonomers.

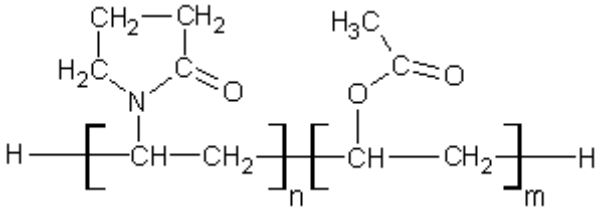


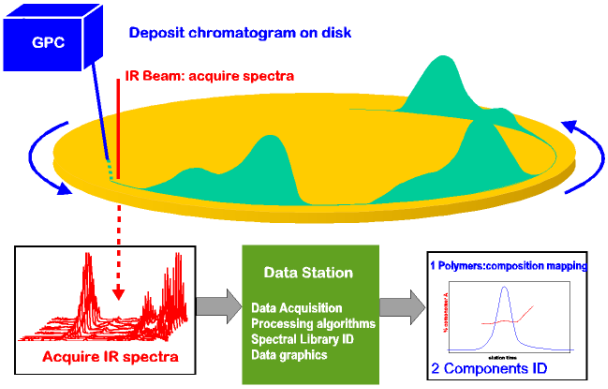
Figure 2 Copovidone chemical structure

When copovidone is co-extruded with an API, a continuous solid phase material results; in which the copovidone acts as a solid dispersant for the API. API/polymer binding typically occurs at the pyrrolidone sites of the polymer chain.

DiscovIR system overview

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 solvent-free 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.



Experimental

We used the DiscovIR LC hyphenated chromatography –infrared spectrometry to obtain some insight as to the heterogeneity of three copovidone samples. Copovidone is produced by several companies worldwide, typically as a 60/40 ratio of VP/VAc. Samples were injected onto a GPC column, and the column eluant flowed to the DiscovIR instrument, where it was deposited as a continuous solvent-free track on an infrared-transparent disk. A set of time-ordered spectra were obtained from the deposit track. Using the data processing software of the instrument, we extracted chromatograms of the maximum intensity infrared bands, and infrared bands centered at1740 cm-1 (acetate) and 1680 cm-1(pyrrolidone).

Sample A is from one manufacturer, and samples B and C are from two production protocols of another manufacturer.

Results

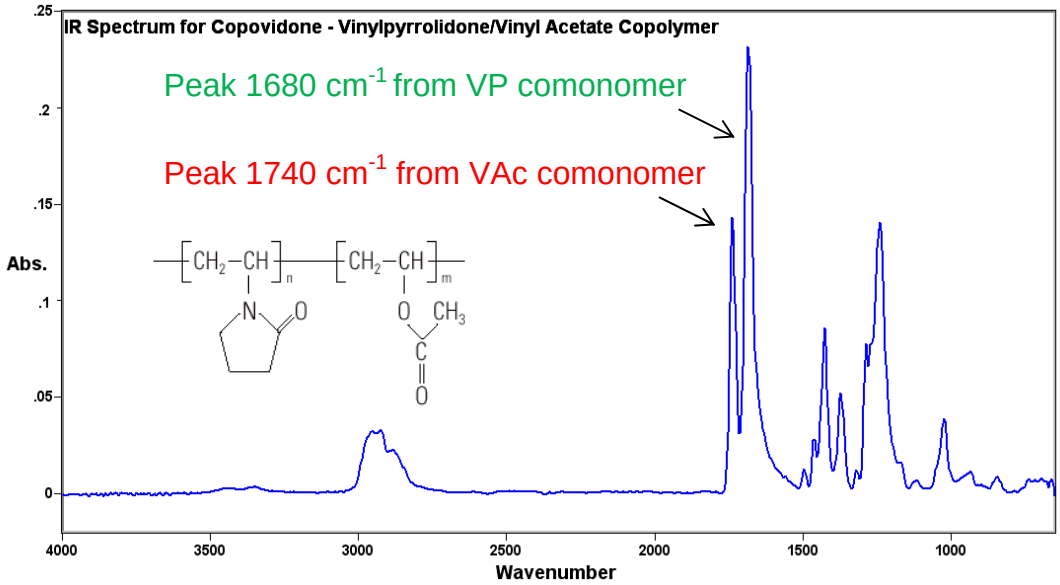


Figure 3 Spectrum of copovidone copolymer

Figure 3 is a single spectrum taken from the DiscovIR run on one of the samples examined. The two comonomers each present strong, well-separated carbonyl IR bands, which were used to track the relative concentrations of the comonomers.

Molecular weight variability of copovidones

The figure below shows the maximum IR intensity GPC chromatograms of the three samples, The horizontal axis display as the log (molecular weight) of the samples.

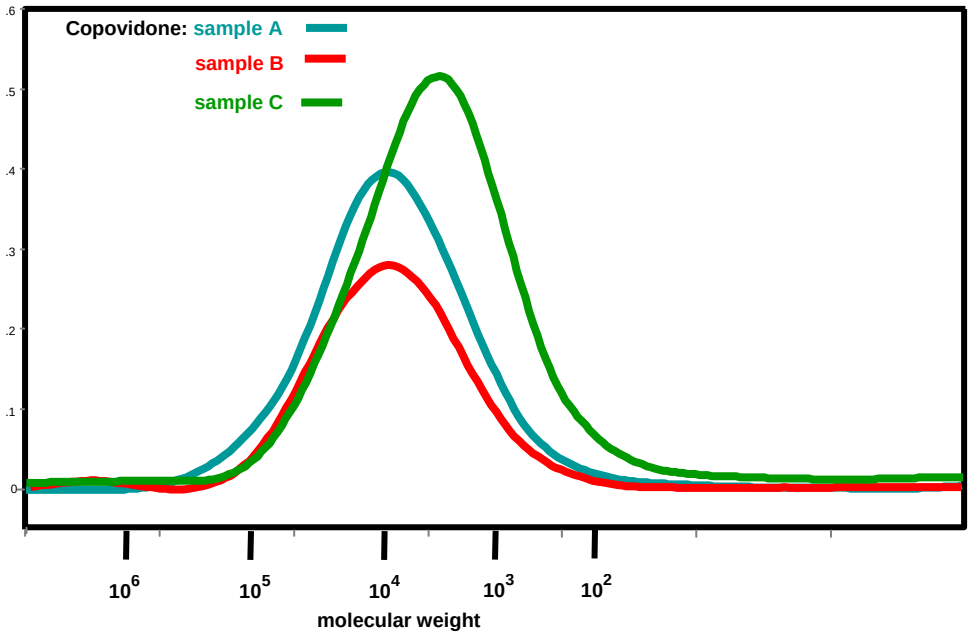


Figure 4 Infrared band chromatograms of the three samples

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- Sample A (vendor 1) is the highest molecular weight of the three samples.
- Sample B (vendor 2) is slightly lower in MW than sample A.
- Sample C (vendor 2) is significantly lower in molecular weight. This sample is approximately one half the molecular weight of the other two samples.

Composition drift: comonomer variation within the samples

A ratio chromatogram was then generated from chromatograms of the infrared bands A_{1740} and A_{1680}. Such a ratio chromatogram effectively cancels the varying mass of polymer along the deposit track, and *reflects solely the changing concentration of the two comonomers*. Algebraic transforms[1] were applied to convert the chromatogram vertical axis to the vinyl acetate comonomer concentration. The horizontal (elution time) axis was expresses as log mw, using the column calibration curve. The following figure is a plot of the concentration of Vinyl Acetate comonomer as a function of molecular weight. All three of the samples were reported as synthesized to a standard 60% PVP/ 40% PVAc bulk composition.

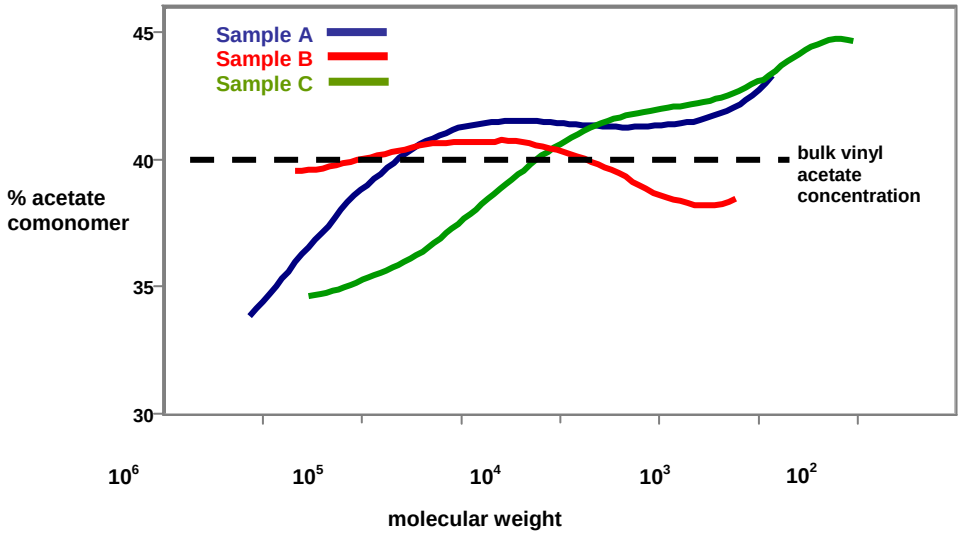

Figure 5 Acetate comonomer relative concentration drift

- Note that the comonomer concentration is not constant across the elution profile (copolymer composition drift). Samples A and C show considerable change in acetate content in the lower molecular weight portion of the GPC eluant.
- Note that the three samples exhibit considerably different comonomer composition profiles.

Lot to Lot variation

Two lots of material "A" were obtained and analyzed for composition variation. As in the previous figure, the data was transformed to a plot of acetate comonomer versus log molecular weight.

[1] DiscovIR-LC Application Note 30, Appendix, July 2009, Spectra Analysis

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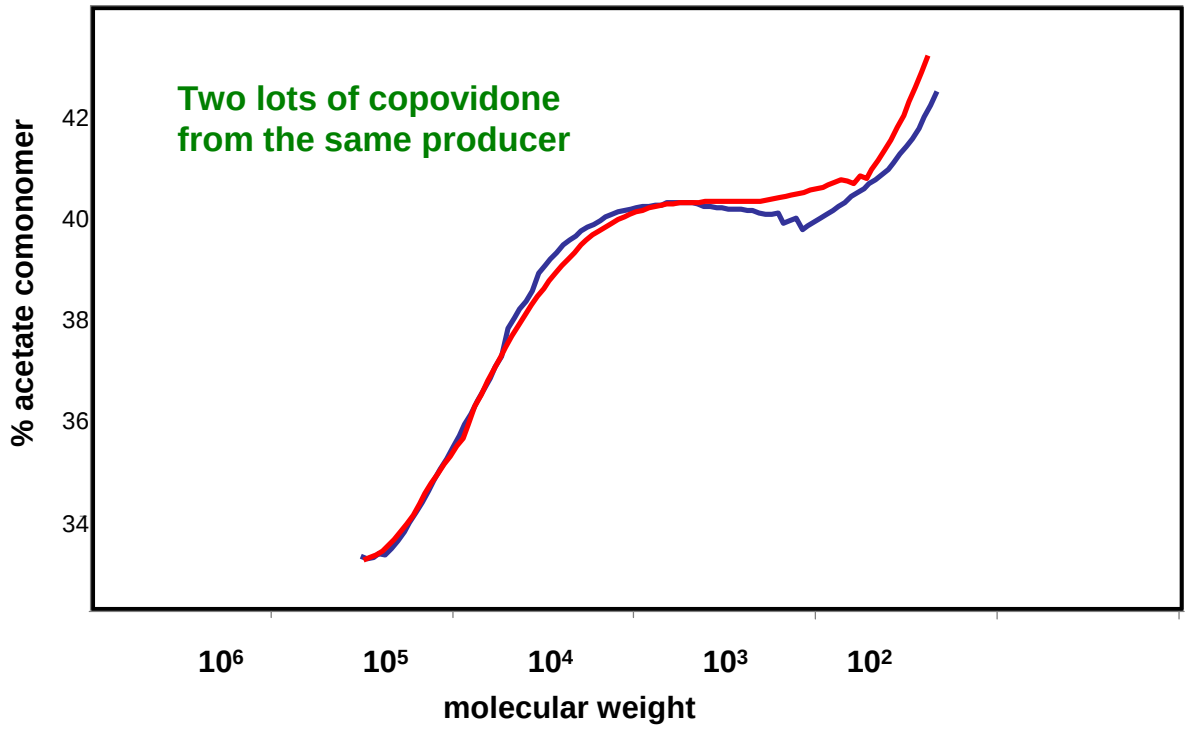

Figure 6 composition variation of two lots of copovidone from one vendor

The composition curves are quite similar, indicating small variation between lots. Both composition and molecular weight profiles of the samples mostly overlap, suggesting a repeatable synthesis process. Further work with such samples can establish whether the observed variations represent actual profile composition changes, or method variation.

Discussion of results

Some copolymer composition drift is the norm rather than the exception in copolymer systems. Reactivity kinetics of two comonomers is rarely identical. In copolymerization operations, if a specific composition profile is desired; it may be obtained by a variety of stratagems, such has stepwise ingredient additions. The manufactures' stated "bulk composition" only addresses overall content of comonomers, and does not address at all the heterogeneity that exists within the population of polymer molecules.

In a similar vein, it is not surprising to find variations in molecular weight distributions, where a simple viscometric value is the only characterization of molecular weight. Realistically one should expect slight lot to lot variations in the molecular weight average and, in some products, differences in polydispersity, possibly accompanied by multimodal distributions.

What does this imply for the critical performance factors provided by polymer excipients? Certainly one should be alert to product performance variability arising from the excipient polymer variation.

Consider the case of a poorly soluble drug combined with a polymer excipient via hot-melt extrusion processing. The API is initially incorporated into the polymer mass as a molecular dispersion within

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the polymer mass. Upon ingestion this polymer-drug matrix is hydrated and swells to form a polymer gel, or viscid mass. The API then is released from the gel by molecular diffusion (through the gel) and/or erosion of the polymer mass. The bioavailability and release kinetics are functions of molecular weight and polymer gel binding (determined by comonomer composition). Release rates are not simple first order kinetics, but rather are an average of the diffusive characteristics and binding equilibria of the drug/polymer mass. If release of the drug is too rapid, the free drug concentration may rise above a critical concentration level; causing crystallization of a poorly soluble API. *Thus both ultimate bioavailability and release kinetics should be a function of the polymer parameters.* If polymers possess batch-to-batch variability, this may well be reflected in drug performance. More thorough characterization of these critical polymeric excipients may well be required for consistent and optimal performance of a finished therapeutic product.

Infrared spectrometry is probably the most extensive and insightful method of analysis of polymer materials. Chromatographic methods, combined with spectrometry, are fundamental in discovering the variability of polymer materials. Increasingly researchers are taking advantage of various chromatographic modes to focus on different aspects of polymer composition and structure. We believe that polymer characterization will prove to be an important tool for determining reproducible controlled release of APIs.

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