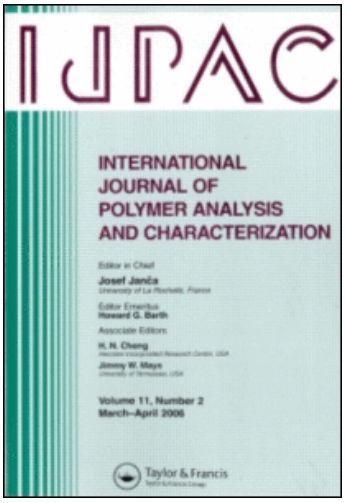


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# Flow Injection Analysis of Polymeric Excipients Used in Pharmaceutical Formulations

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# Flow Injection Analysis of Polymeric Excipients Used in Pharmaceutical Formulations

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**Abstract:** Both hydrophobic and hydrophilic polymer matrices are used in pharmaceutical controlled-release formulations. In order to fully understand the functionality of the polymer in the drug delivery device, it is useful to study both the properties of the material before formulation and the behavior of the polymer in situ. A flow injection size exclusion chromatography approach is described that permits the rapid determination of polymer properties. Examples are given for the application of this method to real-time monitoring of the polymerization of poly(lactide-co-glycolide) and to the study of polymer release from swellable matrix tablets.

**Keywords:** SEC; Flow injection; PLGA; Cellulose derivatives; Intrinsic viscosity

## INTRODUCTION

Polymers are routinely used in pharmaceutical dosage forms in applications such as binders and coatings in tablet formulations and as viscosity modifiers or solubilizing agents in liquid formulations. A particular application area of interest is the use of polymers in sustained- or

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controlled-release dosage forms where the release of the drug is moderated by the selection of specific properties of the polymer.[1] The characteristics of the polymer that influence the greatest degree of control over the rate of release of the active pharmaceutical ingredient in the formulation are molar mass and chemical composition. Both hydrophobic and hydrophilic polymer matrices are used in controlled-release formulations, typified by poly(lactide-co-glycolide) (PLGA) for parenteral administration and cellulose derivatives for oral dosage forms.

Size exclusion chromatography (SEC) is routinely used for the characterization of polymer molar mass distribution.[2] In order to optimize resolution and therefore the accuracy and precision of the measurement, multiple columns are used in series and the pore size distribution is selected to fully resolve all of the sample components across the full anticipated molar mass range of the sample.[3] The system is normally calibrated using a series of narrow polydispersity standards of known molar mass. The typical analysis time for each standard or sample is around 30 minutes, thus the determination of molar mass distribution of one sample normally spans a period of several hours. While this technique provides a reliable method for the determination of molar mass distribution, it does not lend itself to applications where a rapid measurement of such polymer properties is required from the experiment. In recent years, flow injection SEC methods have been applied where it is necessary to make a rapid measurement of polymer properties, for example, in materials discovery where large numbers of samples need to be screened, or in process monitoring where an at-line measurement in near real time is required.[4] This article will illustrate two examples of flow injection SEC analysis applied to two polymer systems, one of which utilizes the advantages of real-time monitoring of polymer properties and a second example where high throughput analysis of a large numbers of samples is required.



## FLOW INJECTION SEC ANALYSIS

The principle employed in this experiment is to derive molar mass rich information not from a high-resolution separation but from the combination of outputs from a concentration detector (differential refractive index, DRI) and a molar mass specific detector (differential viscometer, DV). The SEC system consisted of an integrated degasser, pump, and autosampler unit (GPC Max, Viscotek, USA) connected to a triple detector array (TDA302, Viscotek, USA). For each application, a low pore size SEC column was selected such that the polymer molecules greater than approximately 4,000 g/mol would be excluded from the pores of the packing material but would be well resolved from any residual small molecules (e.g., monomers, additives, solvents) present in the sample.

A relatively short column length was used to facilitate a fast analysis time, thus providing the potential for rapid determinations. The response from each detector can be defined as follows:

$$A_{DRI} = K_{DRI} \cdot c \cdot (dn/dc) \quad (1)$$

where $A_{DRI}$ is the peak area of the DRI detector, $K_{DRI}$ is the DRI detector constant, c is the polymer concentration, and (dn/dc) is the specific refractive index increment for the polymer/solvent combination, and

$$A_{DV} = K_{DV} \cdot [\eta] \cdot c \quad (2)$$

where $A_{DV}$ is the peak area of the DV detector, $K_{DV}$ is the DV detector constant, and $[\eta]$ is the intrinsic viscosity of the polymer (also known as the limiting viscosity number).

First, the two detectors were calibrated using well-characterized narrow polydispersity polymer standards prepared at accurate concentration to determine detector constants $K_{DRI}$ and $K_{DV}$ according to Equations (1) and (2). A reference solution of pure polymer, of the same chemistry and similar molar mass to the polymer under investigation, was prepared and analyzed to determine the (dn/dc) value for that particular polymer/solvent system using the DRI response. In subsequent analysis of samples taken from the process under investigation, this (dn/dc) value was used to determine the polymer concentration from the DRI response, and furthermore the calculated concentration was used to determine $[\eta]$ of a polymer from the DV response.

For a given polymer/solvent system at a constant temperature, the $[\eta]$ of a polymer is directly proportional to the molar mass (M) of the polymer according to the Mark-Houwink equation:

$$[\eta] = K M^{\alpha}$$

where K and $\alpha$ are the Mark-Houwink constants for the polymer/solvent/temperature conditions employed. It can be seen that the output from this flow injection SEC analysis approach is a single measured quantity of bulk intrinsic viscosity for the polymer that is related to molar mass, but no information can be derived about the distribution of molar mass. Therefore this approach is justified for screening the physical properties of the polymer but is not acceptable as a rigorous method for the characterization of polymer molar mass distribution.

## POLYMERIZATION OF PLGA

PLGA copolymers are widely used in pharmaceutical controlled-release systems since they are biodegradable and the by-products of polymer

degradation are not harmful to the patient.[5] The drug and polymer are dissolved together in a suitable solvent and a polymer-drug matrix is produced in the form of a depot or microspheres that can be introduced into the body via subcutaneous injection. The average copolymer composition can be controlled by varying the molar ratio of glycolic acid and lactic acid monomers, and the copolymer is usually produced by a ring opening polymerization of cyclic lactic acid and glycolic acid dimers. The polymerization conditions for PLGA can be varied to give changes in yield, molar mass, and copolymer composition.[6] While the final properties are of primary interest, analytical methods used to monitor the polymerization can provide valuable information for process and product improvements. The aim of this work was to develop a flow injection SEC method and evaluate its applicability to the study of PLGA polymerization reactions to give information on the molar mass and degree of conversion as a function of reaction time under specific conditions. The analytical conditions were as follows:



- Column: PL Rapide-F 150 × 7.5 mm (Polymer Laboratories, UK)
- Eluent: tetrahydrofuran (THF), stabilized 0.025% BHT (Fisher, UK)
- Flow rate: 1 mL/min
- Temperature: 35°C
- Injection volume: 100 μL

The detector constants were determined using a certified polystyrene standard of Mw = 117,100 g/mol, Mw/Mn = 1.03, dn/dc = 0.185 mL/g, and $[\eta] = 0.519$ dL/g, and the dn/dc value measured for pure PLGA copolymers was 0.045 mL/g. At each time point during the reaction a sample of polymer was removed and weighed, dissolved in THF, and injected into the system to determine polymer concentration and intrinsic viscosity $[\eta]$. A retained sample from each time point was also analyzed by conventional high-resolution SEC using a column set of 3 × PLgel 5 μm MIXED-D 300 × 7.5 mm (Polymer Laboratories, UK), THF as eluent at 1.0 mL/min, DRI detection, and a polystyrene standard calibration. A comparison was made between weight-average molar mass (Mw) obtained from conventional SEC and $[\eta]$ obtained from the flow injection analysis (FIA) approach for each time point. Figure 1 shows the raw data chromatograms obtained for samples taken at 5 minutes and at 280 minutes into the reaction. At a reaction time of 5 minutes, there is a relatively high proportion of residual monomer as indicated by the large peak at retention time 5 minutes on the DRI trace, and the polymer concentration and molar mass are both low, hence the area response of both the DRI and the DV detector is low. As the reaction progresses further, the monomer concentration peak decreases and, as both the polymer concentration and molar mass are increasing, both detector responses increase in area.

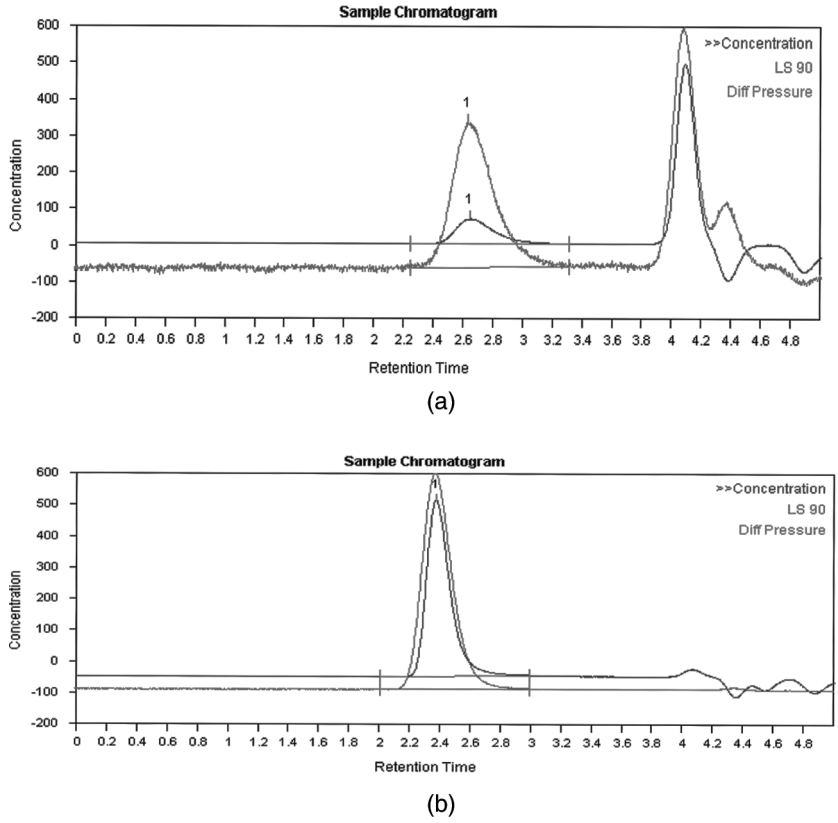




**Figure 1.** Raw data chromatograms from PLGA reaction after 5 minutes (a) and after 280 minutes (b) DRI output is the concentration trace (blue) and DV output is the differential pressure trace (green).

The depletion of monomer and formation of polymer is expressed in Figure 2, which shows a plot of conversion (polymer concentration/total total sample concentration expressed as a percentage) as a function of reaction time.

Figure 3 indicates that the evolution of $[\eta]$ follows a pattern similar to that of Mw as a function of reaction time, but the curves deviate at low conversion. A Mark-Houwink plot is constructed by plotting log M versus log $[\eta]$, which should yield a straight line relationship with intercept log K and slope $\alpha$. However, it has been shown that the Mark-Houwink relationship exhibits a molar mass dependence and shows a decrease in the $\alpha$ value at low molar mass for random coil polymers.[7] As shown in Figure 4 this behavior is observed for the Mark-Houwink plot generated for the PLGA samples taken from the reactor and analyzed by the

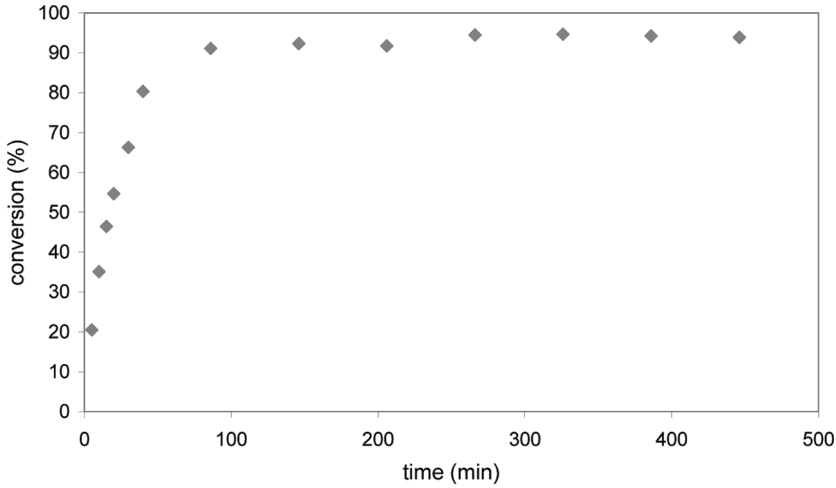


**Figure 2.** Formation of polymer (conversion) as a function of reaction time for PLGA.



flow injection SEC method ([$\eta$]) and by conventional high-resolution SEC (Mw). However, the results do indicate a good correlation between [$\eta$] measured by the flow injection SEC method and Mw measured by conventional high-resolution SEC and suggest that the method would be suitable for comparing the development of polymer [$\eta$] (or implicitly Mw) as a function of time for different polymerization conditions.

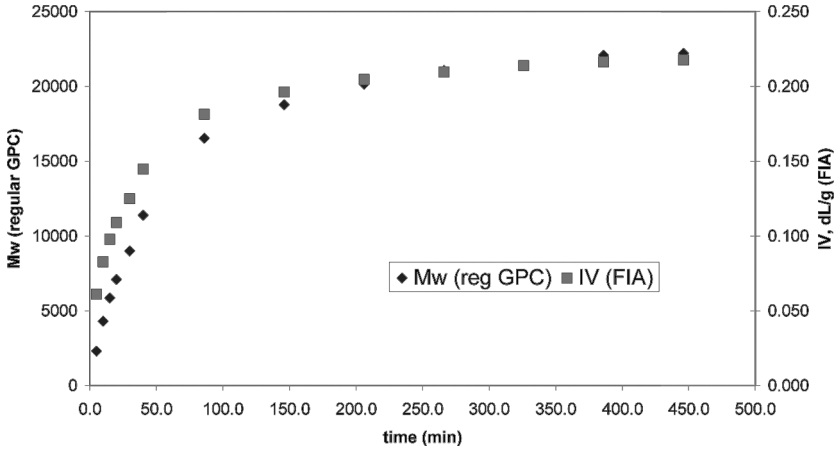


**Figure 3.** Comparison of intrinsic viscosity [$\eta$] (IV) from flow injection analysis and Mw from conventional SEC analysis for PLGA reaction samples.

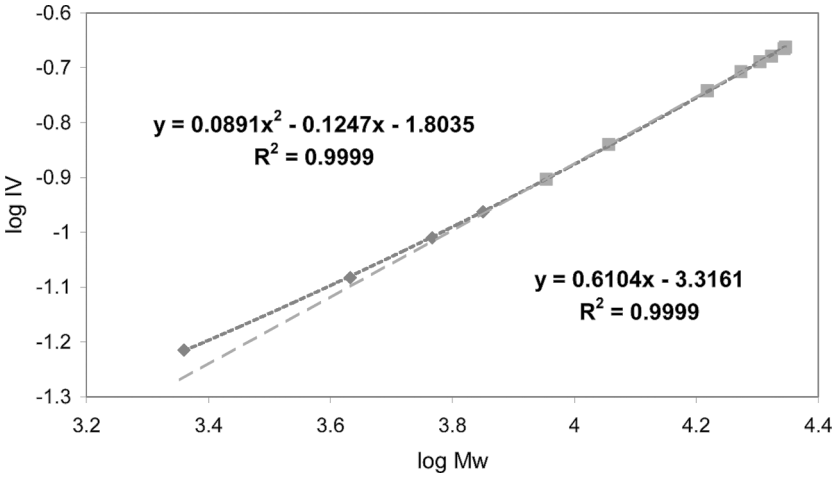


**Figure 4.** Mark-Houwink plot log IV (log [$\eta$]) versus log Mw for PLGA reaction samples, indicating a second-order polynomial fit to all data points (red line) and a first-order polynomial fit to data for data where Mw $>$ 8900 (green line).



## CONTROL OF DRUG RELEASE FROM SWELLABLE MATRIX TABLETS

Swellable matrix tablets provide a method for the controlled release of drugs and are produced by mixing the active pharmaceutical ingredient with a hydrophilic polymer and any other excipients and compressing the contents into a tablet. When the tablet comes into contact with gastric fluid, the hydrophilic polymer hydrates and starts to swell, forming a protective gel layer around the tablet. The release of a drug from swellable hydrophilic matrix tablets can proceed via drug diffusion through the gel layer, by erosion of the gel layer that contains the drug, or a combination of these two processes.[8] The relative rate of diffusion and erosion depends heavily on the properties of the gel layer, which in turn is related to the physical and chemical properties of the hydrophilic polymer used in the matrix. Measurement of the release of both drug and polymer during in vitro tablet dissolution testing is a valuable tool for understanding the mechanism of release from matrix tablets and the effect of the polymer properties on controlling drug release.[9] Normally in vitro dissolution studies of swellable matrix tablets are performed using six tablets (one in each pot), and samples are taken from the dissolution pots at multiple time points over a period of 24 hours, thereby producing a large number of samples to analyze and thus justifying a flow injection SEC approach. The drug concentration in the samples of dissolution media is determined by a UV assay, and, knowing the total mass of drug

contained in the tablet, the amount of drug released as a percentage of the total can be determined as a function of dissolution time. The aim of this work was to develop a flow injection SEC method for the measurement of concentration and intrinsic viscosity of the hydrophilic polymer as it dissolved from the tablet so that the polymer release could be compared to the drug release profile. The analytical conditions were as follows:

- Column: Ultrahydrogel 120 $300 \times 7.8$ mm (Waters, USA)
- Eluent: dissolution media, phosphate buffer
- Flow rate: 0.8 mL/min
- Temperature: 30°C
- Injection volume: 100 μL

The detector constants were determined using a pullulan polysaccharide standard of Mw = 112,000 g/mol, Mw/Mn = 1.20, dn/dc = 0.143 mL/g, and $[\eta] = 0.258$ dL/g, and the dn/dc value measured for the pure polymer used in the formulation was 0.130 mL/g. For each time point in the dissolution test, the six replicate samples were analyzed to determine the percentage of the total polymer released from the tablet and its intrinsic viscosity, which is related to molar mass. Figure 5 illustrates a typical data set where the average value of percentage polymer released is plotted as a function of dissolution time alongside the average drug release data. In this case the rates of release of drug and polymer were found to be very similar, indicating that the release mechanism from the matrix tablet was

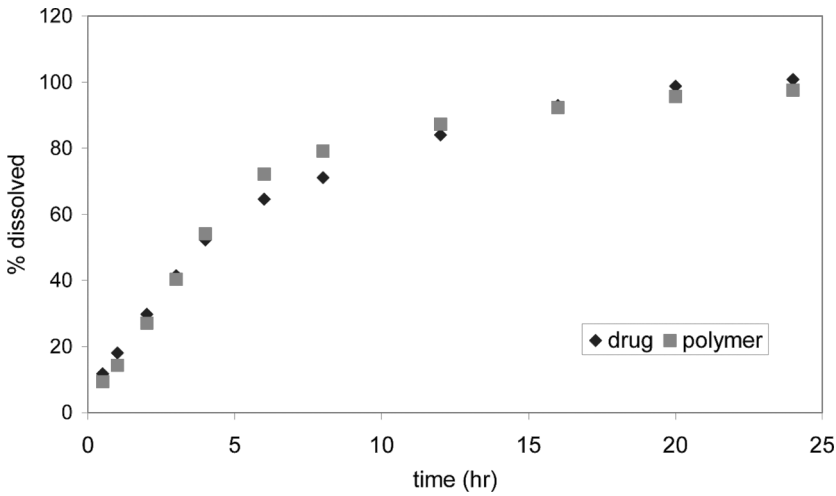


**Figure 5.** Dissolution rates for drug and polymer from in vitro test.

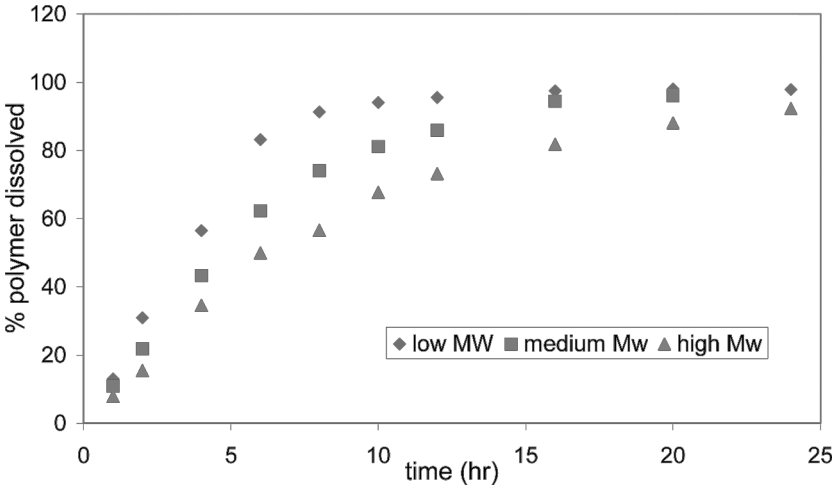


**Figure 6.** Effect of molar mass on polymer dissolution rate.



predominantly controlled by erosion of the gel layer. Three matrix tablet formulations were studied where the molar mass of the hydrophilic polymer was varied, and the polymer dissolution data are shown in Figure 6. The rate of polymer release (and drug release since the mechanism remained consistently erosion controlled) was found to be molar mass dependant, which is consistent with results reported in the literature.[10] The low molar mass polymer

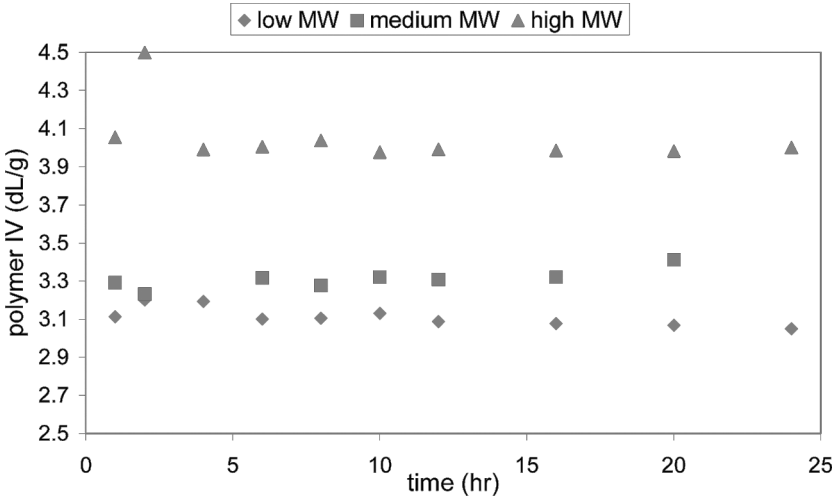


**Figure 7.** Intrinsic viscosity [$\eta$] (IV) of polymer released during dissolution test.

releases faster than the high molar mass polymer due to an increased rate of chain disentanglement at the eroding gel front.[8] Figure 7 shows that irrespective of the molar mass of the polymer in the formulation, the [$\eta$] of the dissolved polymer was uniform at all time points in the dissolution experiment, suggesting consistent erosion of all chain lengths at all times.

## CONCLUSION

Flow injection SEC analysis permits the rapid determination of polymer properties, specifically as described here the bulk intrinsic viscosity, which for high throughput of samples or process monitoring offers a distinct advantage over more conventional SEC methods. An alternative approach could be to use a light-scattering detector rather than a viscometry detector since the intensity of scattered light is directly proportional to molar mass. However, the sensitivity of light-scattering detection is low for polymers with low molar mass, low dn/dc, or low concentration in solution, which limits its applicability to the two polymer systems described. The flow injection methods outlined here show that this approach is applicable to both organic and aqueous soluble polymers and to polymer systems that are relatively complex and contain significant quantities of other components. This latter feature is very useful for the analysis of polymeric excipients in situ in pharmaceutical formulations, although it is recognized that for thorough characterization of polymeric excipients as raw materials, conventional high-resolution SEC is required.



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