DEVELOPMENTS IN EVAPORATIVE LIGHT SCATTERING DETECTION FOR THE DETERMINATION OF IMPURITIES IN ACTIVE PAHRMACEUTICAL INGREDIENTS

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ABSTRACT

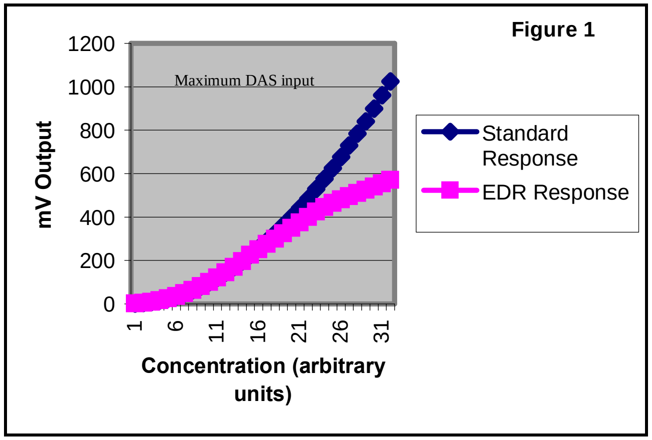
Impurities in pharmaceuticals, the unwanted chemicals that remain with the active pharmaceutical ingredients (API), may influence the efficacy and safety of the product, even in small amounts. Identification of these impurities at levels above 0.1% is usually required by regulating agencies. An HPLC detector must have a dynamic range greater than 3 to quantify the API and still detect the 0.1% impurity. Evaporative Light Scattering Detectors (ELSD) are ideal for detecting unknown impurities because they respond to all compounds that are less volatile than the HPLC mobile phase. ELSDs nebulize the column effluent, transforming it into an aerosol cloud. As this cloud travels through a heated zone within the instrument, the more volatile mobile phase evaporates, leaving the smaller cloud of analyte particles. These particles pass through a beam of light, scattering some of the light, which is converted into an electronic signal. Any particle in the column effluent less volatile than the mobile phase will produce a response from the detector. Many ELSDs do not have 3 orders of magnitude and require the range or gain be changed mid-run to identify the impurity in presence of the product. But the nature of the impurities frequently does not allow identification of retention times for time-based changes. We have developed an ELSD with extended dynamic range to respond to this need.

The Goal: **An ELSD with 3+ orders of magnitude dynamic range, under typical HPLC conditions.**

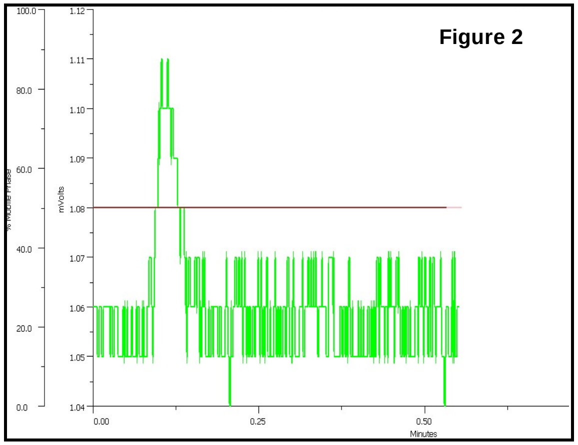
The Problem: **Both the typical ELSD, and the typical Data Acquisition System (DAS) have limitations which hinder wide dynamic range.**
Specifically:

1. **All ELSDs exhibit non-linear response to increasing analyte concentrations. As concentration increases, response increases much faster. This limitation is inherent in the physics of light scattering, and is independent of instrument design. See Figure 1**
2. **Many DA systems exhibit considerable digitizing noise at very low signal levels, so even though an instrument might be more capable, it must supply at least 100 uV of signal in order to be compatible with low concentration detection goals. In practice, one mV is a safer threshold. Additionally, most DA systems have a 1V maximum input signal. These limitations prevent simply scaling down the instrument output, or allowing a higher voltage output as techniques for extending dynamic range. See Figure 2**

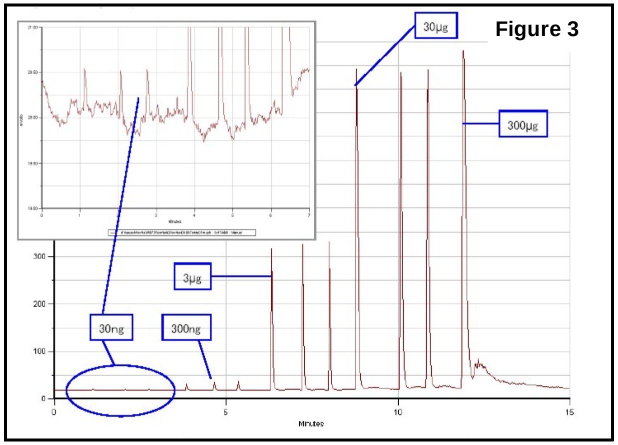
The Solution: **A variable feedback electronic amplifier following the detector element (silicone photodiode) selectively attenuates large signals, while allowing low level signals to pass untouched. In our implementation, (Extended Dynamic Range) the larger the original signal is, the more it is attenuated. See Figures 1&3.**



Low level signals pass through EDR circuitry.
Higher level signals experience smooth attenuation.



Lower limit imposed by Data Acquisition System
(Digitizing noise of DAS becomes prominent)



3+ orders of dynamic range using EDR.
(Courtesy of Yuichiro Hayashi, M&S Instruments)