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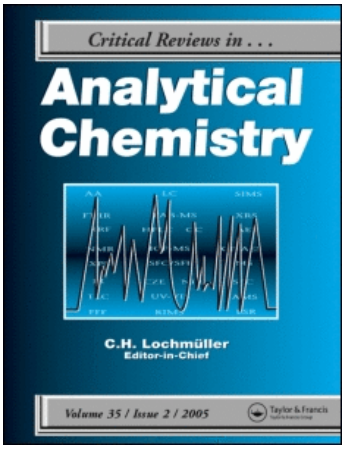

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On the Issue of Characteristic Evaporative Light Scattering Detector Response

Krystyna Mojsiewicz-Pieńkowska[a]
[a] Faculty of Pharmacy, Department of Physical Chemistry, Medical University of Gdańsk, Gdańsk, Poland

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On the Issue of Characteristic Evaporative Light Scattering Detector Response

Krystyna Mojsiewicz-Pieńkowska
Medical University of Gdańsk, Faculty of Pharmacy, Department of Physical Chemistry, Gdańsk, Poland

In recent years, the evaporative light scattering detector (ELSD) has increasingly been used in conjunction with liquid chromatography for detection of various analytes. Due to the specificity of the detection method, which is based on the scattering of laser light on the non-volatile analyte particles, the ELSD has been considered a universal detector. This article presents issues concerned with the response of this detector. A review of experimental results presented by researchers who used the detector in question clearly show that two major issues tend to recur. Interestingly enough, the researchers do not have a uniform opinion on those issues. First, the majority of authors treat the detector signal as a mass signal, i.e., the response is believed to depend only on the analyte mass. Second, a number of different approaches are offered to analyze how the detector signal depends on analyte mass.

Keywords Evaporative light scattering detector, detector response, linearity, calibration

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INTRODUCTION

After scrutinizing research results presented by various researchers using an evaporative light scattering detector (ELSD) for liquid chromatography, we can observe two important issues concerning the detector response. The first relates to the fact that a majority of researchers consider the detector signal to be a mass signal. It is widely believed that the response of the ELSD depends on the mass of the analyte. Therefore, many authors believe that this detector does not need any specific calibration for particular analytes but that a "universal" calibration curve can be used. In this paper we raise the question whether this is at all possible for a ELSD used for the analysis of different compounds. The second issue concerns the relationship between the ELSD response and the mass of the analyte, as this is presented differently by different researchers. Experimental evidence suggests that the detector response is non-linear, i.e., constituting a considerable limitation or drawback in quantitative studies. In the present paper, we review how different researchers have tackled this problem of non-linearity, and whether this was considered to be a drawback that significantly influenced quantitative determinations and the magnitude of the error. In order to relate our own opinions to the existing publications, a few findings considered to be crucial for this issue are discussed.

Address correspondence to Krystyna Mojsiewicz-Pieńkowska, Medical University of Gdańsk, Faculty of Pharmacy, Department of Physical Chemistry, Al. Gen. Hallera 107, Gdańsk 80-416, Poland. E-mail: kpienk@amg.gda.pl

UNIVERSAL OR NON-UNIVERSAL CALIBRATION CURVE

Results published by J. M. Charleswarth (1) in 1978 represent the first detailed study on the characteristics of this type of detector. The author studied five different compounds which may occur as a result of polymers generation, e.g.,: p,p′- diaminodiphenylmethane (DDM), di-glycidyl ether of bisphenol A (DGEBA), a product of reaction between n- methylaniline (NMA) and DGEBA, a reaction product of phenyl glycidyl ether (PGE) and aniline (ANIL), and the reaction product of NMA and PGE. Charlesworth studied the dependence of the detector response on the concentration of the investigated analytes, expressed as the peak area. In the study, concentrations between 7.5×10^{-5} and 3.0×10^{-3} g/cm^3 were used. For all the compounds studied a very similar dependence was found, which for the whole range of concentrations was non-linear. In his conclusions, Charlesworth stated that the calibration curve is approximately linear for concentrations between 1×10^{-4} and 1.5×10^{-3} g/cm^3, and that the detector response does not depend on the chemical structure of the compounds. He suggested that the detector may be treated as a mass device and can be used to determine concentrations of variable compounds without previous preparation of separate calibration curves.

A. Stołyhwo et al. (2–4) used a ELSD detector for the analysis of lipids. He proved that the dependence of the detector signal on the mass of the analyte is different and non-linear for various constituents. He also showed that the results could be fitted to a log/log line with a slope of 1.82. He described the detector

response function by a power function (1) similar to the one proposed by Fowlis and Scott (5):

$$D = k\,C^x \quad [1]$$

where D is the measured value, e.g., peak area, k is the proportionality constant called the coefficient of the detector reaction, C is the concentration of substance in the mobile phase (or substance volume) and x is the coefficient (exponent).

The author added that the value of the coefficients k and x depend on nebulization conditions and evaporation of the mobile phase, as well as on the chromatographic system and some properties of the solvent.

The value of x for a linear function equals 1, and for the nonlinear function the values ranged from 1.32–1.82, depending on the technical solutions used in the nebulizer. For fatty acid methyl esters with a chain length between C_{14} and C_{18},the signal proved independent of molecule size. From the experiments carried out, it became clear that the detector response is generally the same for the various components analyzed and that it depends neither on their molecular weight nor the saturation ratio. Similar measurements carried out on groups of chemical compounds with markedly different structures, e.g., triacetylglycerols, phthalates, polynuclear hydrocarbons, and polystyrenes of variable nuclear weight, confirmed the regularities obtained from analyses of the fatty acid methyl esters.

However, deviations from these regularities were observed for substances with lower boiling temperatures, e.g., methyl myristate (Me $C_{14:0}$) or ethylene glycol. This could be related to evaporation of these components during the nebulization. Similar irregularities were observed for methyl ester of eicosanoate acid ($C_{20:0}$), which has a higher melting temperature than fatty acid methyl esters. In publication (6), R. Devereaux's (Richard Scientific, Inc.) words were cited that he also claims that it is possible to use one common calibration curve. The author pinpoints that the lack of necessity to make individual calibration curves for particular analytes makes the detector a fast device for assessment of the purity of synthetic organic compounds, which is a great advantage in comparison with, e.g., a UV detector.

B. Trathnigg and Kollroser (7), in their experiments with polyethylene glycols and their derivatives, also described the calibration curve as a power function. He noticed that there is no difference between hexaethylene glycol, PEG 1000, and lower oligomers.

L. Fang et al. (8) also came to the conclusion that the laser light-scattering detector can be used as a universal detector for fast determination of various analytes. The author selected a wide range of compounds with different structures, such as nonaromatic heterocyclic compounds (hydrofuranes, izoxazolines and oxadiazolines), aromatic heterocyclic compounds (indoles, quinolines, oxadiazoles and izoxazoles) and other important groups like arylic sulfonamides, arylic amides and guanides. In order to obtain a common relationship between peak area and mass in the concentration range of 0.1–3.0 μg/L, Fang applied the logarithmic transformation and obtained a coefficient of determination equal to 0.99. These experiments showed that the detector may be used universally for fast determination of complicated chemical compounds with 20% average error for various structural groups.

J. L. Sims (9), in his 2001 publication, claims that the laser light-scattering detector can be used as a mass detector. The author also presents a test which, according to the author, can be used both for validation of the detector and for substitution of an existing test based on alpha-d-glucose, which is enclosed in the Sedex 55 detector manufactured by Richard Scientific, Inc. (Novato, CA, USA) in Alfortville, France. Sims claims that alpha-d-glucose is unstable in solutions and therefore not suitable for verification whether a given detector complies with requirements or not. In order to verify the suitability of a particular detector with respect to noises and level of determinability, the author selected caffeine, and carried out tests using a detector of the type Sedex 55. This was, according to the author, the best compound when considering both stability and price. Still, it was underlined that application of this test requires setting of the appropriate pressure of the nebulizer gas and temperature, as those parameters influence the signal intensity. Also, the indicated determinability level for caffeine (85 ng) is strictly limited to this type of ELSD detector.

K. Rissler presented a review (10) of studies using HPLC and various detection methods (including ELSD) for the analysis of polyethers. Speaking about the problem of quantitative analysis he pinpointed that authors such as S. Brossard et al. (11) and A. Stołyhwo et al. (3) observed almost identical detector responses for higher polyethylene glucol (PEG), fatty acids, methyl esters, triglycerides, and cholesterol. Those authors have suggested that the signal intensity solely depends on the analyte mass, and to a great degree is independent of its chemical constitution. The validity of this suggestion has been confirmed for at least similar classes of compounds.

They believed that this means that it would be possible to carry out quantitative determination of polyethers directly from the peak areas, avoiding the need to prepare separate calibration curves for different analytes. In spite of this advantage, the scientists recommended making individual calibration curves for particular compounds, as different responses may occur even in one class of compounds. This was observed for the following polar lipids: phospholipids, sphingomieline, and cardiolipins, which all gave a signal four times higher than the other compounds analyzed (3). Stołyhwo observed differences in the detector response between compounds belonging to the same chemical group, but with different states (solid or liquid) during the detection. He claimed that the "snow flake" type of compounds scattered the laser beam more strongly and therefore resulted in a four-time increase in the signal in comparison with compounds of the "rain drop" type. K. Rissler also mentioned other observations which other authors saw (10). A. I. Hopia and V. M. Ollilainen (10), as well as Brossard et al. (11) , observed a slight influence of the chemical structure on the detector response for mono- and trioleins. However, when using a calibration curve

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made with trioleins to determine PEG 1000, unsatisfactory results were obtained for lower concentrations while for higher concentrations the results were close to the expected values. K. Rissler suggested that even though in many cases a universal calibration curve cannot be used for compounds that differ in chemical structure, it is workable for the analysis of compound classes of similar structure. In Rissler's publication other papers are cited, in which the authors have widened the discussion about factors influencing the response of ELSDs. L. E. Oppenheimer and T. Mourey (12) and P. Meeren et al. (13) observed differences in detector response between various analytes, and their explanation was that many factors influence of the signal (e.g., the coefficient of refractometery and the density and shape of sample molecules). For this reason they believed that it is necessary to make individual calibration curves for different compounds. B. Toussaint et al. (14), B. A. Avery et al. (15), R. Niemi et al. (16), P. Juanéda et al. (17) and R. P. W. Scott (18) came to similar conclusions.

Quantitative analyses of pulmonary surfactants phospholipids using a ELSD were carried out by H. Bünger and U. Pison (19). In this publication, there is also information about the non-linearity of the calibration curve. The authors stated that the value of the exponent in the power function (Eq. 1) was similar for nine tested classes of phospholipids in the range 1–25 μg, and amounted to 1.83–1.63, with a mean value of 1.73, and standard deviation equal to 0.07. After transformation to the logarithmic scale, the linear calibration curves obtained from different phospholipids had almost the same slopes. The authors emphasized that for selected phospholipids calibration curves were determined in the log/log system in spite of a similar value of the exponent a, which determines the slope of the calibration curves. Bünger stated that differences in the established parameters of the calibration curves may have resulted from different peak shapes and non-linear detector response. The author believed that in order to increase the accuracy of the analysis, separate calibration curves for each class of phospholipids should be prepared.

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LINEAR OR NON–LINEAR DETECTOR RESPONSES

Another issue brought forward in the introduction of this paper concerns the dependence of the evaporative light scattering detector signal on analyte mass, as presented by various authors. In the majority of publications, the authors spoke about a non-linear dependence of the signal on concentration. Such results were described by several authors: C. Henry (6) S. L. Hansen et al. when analyzing triacyloglycerols (20), V. Verhelst and P. Vandereecken in a publication (21) on organosilicone copolymers, S. Morera Pons in a study of human milk triacyloglycerols (22), L. Carbognani (23) in an article on fast control of C_{20}-C_{160} alkanes in raw oils, S. Deschamps et al. when investigating the possibility to upgrade the detector response by addition of formic acid (24), I. Clarot et al. (25) when analyzing gentamicine sulfates, Q. Zhou and L. Zhang (26) in their quantitative tests on ceramides, J. L. Sims (9) in study of validation tests, and many others. Similar conclusions were also reached by B. Toussaint et al. (14), who tested the linearity when determining the (S) and (R) enantiomers of 3-tert-buthylamino-1,2-propanodiol. Their review of other publications on the subject confirmed the non-linear character of the detector, and subsequently they presented different approaches to the issue of non-linearity. From the test results, a standard curve was made for (S)-3-tert-buthylamino-1,2-propanodiol in the range 50–1500 μg/ml, and the following equation was obtained: $y = 0.8564\ x^{1.6534}$, where the coefficient of determination (r^2) equalled 0.9988.

Toussaint et al. emphasized that the lack of linearity does not exclude the possibility to use their detector for quantitative analyses. For quantitative determinations they suggested alternative solutions. The first is based on the fact that all non-linear curves include an interval, where the determinations give a linear response. Consequently, they chose a narrower range of concentrations from 500 to 1000 μg/mL. Results from this range were adjusted to a rectilinear progression of the following form: $y = 1.3723\ x + 0.1723$, where y is the logarithm of the peak area, and x is the logarithm of the analyte mass. The coefficient of determination equalled 0.9995. Toussaint et al. claimed that the coefficients a and b depend on the nebulization and evaporation of the mobile phase conditions, the concentration ranges and the properties of the dissolved substance. An alternative solution to the problem of non-linearity is based on the application of the following quadratic equation: $y = ax^2 + bx + c$, where y is the logarithm of the peak area, and x is the logarithm of the analyte mass. The logarithmic transformation of the results allowed a good fit of the results to the quadratic equation: $y = -0.1349x^2 + 1.7418x - 0.00845$. For the whole range of concentrations between 50–500 μg/mL, the coefficient of determination equalled 0.9996, which is a great advantage and promotes this sort of solution. Another advantage of this model is that there is no need to dilute the samples before the analysis. Toussaint et al. carried out similar quantitative tests for (R)-3-tert.-buthylamino-1,2-propanodiol. Comparing test results with those of other selected analytes they noticed that the peak areas differed considerably though the concentrations were the same, but the reason for these differences in the detector response remained unidentified. They believed that it is not possible to use a common calibration curve for many different analytes.

B. A. Avery with his co-workers (15) made experiments with fast detection of artemisin (anti-malaria drug) and its analogues, and used [similarly as Stołyhwo et al. (2–4)], a logarithmic calibration curve based on the dependence of the peak surface area on the concentration. The concentrations ranged from 7.5 to 40 μg/ml. For each artemisin analogue he determined a separate regression curve (though the compounds structures are similar), which was used for the quantitative analyses.

S. Morera Pons et al. (22) confirmed that in some publications the authors described a linear detector response for a wide range of concentrations. However, many authors have claimed that the response of this mass detector is non-linear and is described by a power function. In analytical tests of five classes

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of triglycerides included in the human milk, S. Morera Pons presented calibration curves for the concentration ranges 1–500 μg as linear regressions and equations containing power functions. The coefficient of determination for the dependence of the signal on the analyte mass, formulated as a power function, equalled 0.999, and for the linear regressions had various values for different analytes, ranging from 0.973–0.981. S. Morera Pons carried out tests with two internal standards: triundecanoin and trinonadecanoin. The author concluded that due to slight differences in the calibration curve parameters between the internal standards and the triglycerides analyzed, a quantitative analysis can be carried out based on the method prepared. Another author, R. Sala, was cited (22) as having shown statistically significant differences between two suggested internal standards, yet different than those used by Morera Pons. R. Sala claimed that this discrepancy does not refer to structure but results from considerable differences in retention time of triglycerides.

M. K. Manoj Babu (27) investigated the quantitative determination of four anti-epileptic drugs including Piracetam, VPA-Na, Primidon and Carbamazepine. The dependence of the detector response on the mass of the analyte, expressed as peak area, was described as a logarithmic relationship: Log (x) = log (b) + a log (m) where x is peak area, m is analyte mass and a and b are detector coefficients. For four independent calibration curves, the determination coefficient varied between 0.9951 and 0.9986. The value of coefficient a ranged from 1.4118–1.7463, and that of coefficient b between 5.0466–5.7835. It is worth noting the similarity of both the a-coefficient, responsible for the slope of the curve, and the b-coefficient, determining the OY-axis intersection point.

R. Niemi et al. (16) determined clodronate (a compound that belongs to a group of derivatives of biphosphoniane acid) and its ester derivatives and also dealt with the issue of detector response linearity. He tested linearity in a system of isocratic and gradient elution. All calibration curves were non-linear and were evaluated by a quadratic equation with a very high coefficient of determination (r^2 = 0.999–0.1000). Based on the experimental results the author inferred that both the chromatographic conditions (though to a lesser degree) and the structure of the analyte itself influence the detector response (and therefore differences in the calibration curves for clodronate and its phenyl ester occur). R. Niemi et al. referred to the conclusions by other scientists that the detector response increases sigmoidally with an increase in the mass of the analyte. This dependence was often presented as a linear or a power function. The researchers claimed that the detector response is additionally influenced by the chromatographic conditions, detector parameters, as well as the chemical structure of the analyte itself.

Quantitative determination in HPLC in connection with ELSD was also studied by L. Wenkui and J. F. Fitzloff (28), in their tests on 24(R)-pseudo ginsenoside. Several methods were used for linearization of the detector response. The authors presented a linear calibration curve after logarithmation, but also a quadratic equation. Interestingly enough, logarithmically converted results presented in the form of a quadratic equation resulted in the most expedient calibration curve. This was proven by the shape of the calibration curve and the value of the coefficient of determination.

T. Schunk was cited (6), and suggested another solution to this troublesome aspect of the detector, i.e., the non-linear response to analyte mass, and proposed the use of second-degree and third-degree polynomials.

Similarly, R. Vogel et al. (29), in a publication on determination of isepamicine sulfate, presented detector linearity by means of a third-degree polynomial, and even fourth-degree polynominal.

In the references gathered for this review, several publications showing a linear dependence of peak area on sample mass were found. Such a dependence was described by P. Juanéda et al. (17) for the analysis of six classes of phospholipids of rat livers and hearts. Concentrations for phosphatydylocholine and phosphatydylethanolamine ranged between 750–3500 μg/mL, and for phosphatydylinozytol and phosphatydylserine between 100 and 600 μg/mL. However, the value of coefficient a varied considerably, from 0.274 to 0.971, and hence Juanéda et al. emphasized that each class of phospholipids requires an individual calibration curve.

C. Silversand and C. Haux (30) also showed a linear dependence between peak surface area and the mass of both polar lipids (sphingomieline, di-phosphatydylglicerol, phosphatydylserine) and inert lipids (triacyloglicerol, free fatty acids, monoacylglicerol) tested in fish meat. The linear dependence included approximately all polar lipids in the range 2–20 μg with the determination coefficient r^2 = 0.98–1.00, whereas for inert lipids in the range 0.8–5.0 μg, the determination coefficient was r^2 = 0.98–0.99. The various ranges for these two classes of lipids indicate a more intensive scattering of the light, and thus a higher detector response, for inert lipids. Moreover, the different slopes of the calibration curves also proved that there are differences in the detector responses. This was observed not only between the selected classes of polar lipids and inert lipids but also within a given class. This again highlighted the necessity for preparation of individual calibration curves.

Many authors, e.g., A. Stołyhwo (2–4), C. Henry (cited in 6), R. P. W. Scott (18), and S. L. Hansen (20), were of the opinion that the non-linearity of the ELSD response is a drawback. Charlesworth (1) performed detailed experiments to show that multiple factors influence the signal generation and result in the non-linearity of the detector. He believed that the sigmoidal shape of the calibration curve is influenced by four processes (Rayleigh scattering, Mie scattering, reflection and refraction), due to which the electromagnetic radiation tract may change direction when passing through a medium. The importance of each of the processes depends on radius (r) of the molecule compared with the light wave-length (λ).

CONCLUSIONS

This literature review does not allow a unique conclusion as to whether it is suitable to use a common calibration curve for quantitative analyzes of different analytes using the ELSD. This issue is very complex and individual scientists express various opinions. Having analyzed the arguments of those authors we can distinguish three main options:

a) A common calibration curve can be used for compounds that differ in chemical structure and properties;
b) A common calibration curve is possible to use only for compounds of similar chemical structure and similar properties;
c) Individual calibration curves have to be made in each case.

In spite of the fact that some researchers tend to believe that the ELSD is a universal device for detection of various compounds, and that the detector response depends on analyte mass only and not on chemical structures, the opinion that it is necessary to prepare individual curves for each substance to be determined seems more convincing. One cannot neglect the experiments that resulted in different detector responses (though the differences were not significant) for compounds of the same structure. This must be connected with the complicated mechanism of signal generation and the many factors that influence this mechanism, even though the measurement method is simple. Considering the issues of detector operation, we have to refer to existing theories describing the scattering phenomenon, i.e., Rayleigh and Mie scattering, reflection and refraction. The analyst realizes how tempting the possibility to use the same calibration curve is. This simplifies and accelerates the analysis and at the same time limits the possibility of committing mistakes in the analysis. For groups of similar compounds this can be considered, still detailed tests have to be carried out, and a common calibration curve has to be used only under strictly specified measurement conditions. This means using the same detector operation parameters, e.g., pressure of nebulizing gas, temperature of the drift tube and mobile phase flow. Their influence on the signal formation is significant. However, such decisions depend on the analyst and the properties of the group of compounds to be analyzed, as it is known that considerable differences in detector response may occur within one group of chemicals.

Considering the problem of detector linearity, it can be inferred that the lack of linearity does not constitute a factor that excludes using the detector in question for quantitative purposes. There are still possibilities for linearization of the signal dependence on analyte mass. It is important that the function of this dependence is monotonic and strictly defined, i.e., described by an equation such that the coefficient of determination, which describes the strength of the signal dependence on mass of analyte, is close to 1. In the studies reviewed, the authors achieved this goal by means of various equations, based on which they were able to obtain accurate results from their analyses. Furthermore, those results also confirmed the fact that non-linearity is not a drawback or limitation, but a characteristic feature of this detector. This opinion has also been confirmed by multiple applications in analytics, and a growing interest in this detector. From the cited references, many consistent and favorable opinions concerning a general strategy for quantitative studies have been found.

Papers referred to in this study confirm the fact that a linear dependence of the detector response on analyte mass (though already described) constitutes an exception rather than a rule for this type of detector. Generally, if a linear range has been observed, it is very narrow. The non-linear response is most often described by a power function (Eq. 1). The value of the numerical coefficients k and x are related to the nature of the mobile phase and to detector parameters (25), but also to the molar mass of the analyte (7). The exponent x is additionally strictly related to the shape of the nebulizer (22), pressure of the carrier gas and the conditions for evaporation of the mobile phase. Generally x takes the values of 1 to 2, depending on the apparatus used. If it is equal to 1, the dependence becomes linear.

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