



Review

Potential of high temperature liquid chromatography for the improvement of separation efficiency—A review

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ABSTRACT

This review has been written in the context of critically evaluating the potential of high temperature liquid chromatography for the improvement of separation efficiency. The focus of this review is also laid on a critical evaluation of the applicability of this technique in a regulated environment. The review tries to give an overview over all aspects which can lead to a deterioration of the separation efficiency. This means that the discussion is not limited to a theoretical treatment of the van Deemter equation, but that all aspects which can contribute to a loss of efficiency are covered. This includes the design of the heating equipment as well as the possible degradation of the stationary phase or analytes. Therefore, the review is also a general review which tries to include the latest findings on high temperature HPLC. Also, temperature programming is critically evaluated. It is outlined that this technique is a prerequisite for certain hyphenation techniques like isotope ratio mass spectrometry or flame ionisation detection. However, it is critically discussed if temperature programming also will improve the separation efficiency.

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1. Introduction

The potential of high temperature liquid chromatography has been discussed in the scientific literature for more than 30 years [1]. Nowadays, high temperature liquid chromatography is of renewed interest. In 2007, a special issue of the *Journal of Separation Science* has been partly devoted to high temperature liquid chromatography and many contributions therein deal with high temperature HPLC [2–8]. It is therefore of interest to ask why the use of temperature as an active variable for the improvement of the separation efficiency has not been implemented in industry up to now. Certainly, some technical drawbacks have prevailed as yet. However, great progress has been made if the stationary phase or the heating equipment is concerned. Nevertheless, the problem of analyte degradation is discussed controversially. Especially in the pharmaceutical industry this is a serious issue, although it was demonstrated theoretically [9,10] and experimentally [11] that this fear might be overestimated.

In this review, the application of high temperature liquid chromatography is critically evaluated and discussed in terms of using this method in a regulated environment for the improvement of separation efficiency. Although there are a number of reviews which have been published in the last years and which also cover important aspects outlined in this review [12–17], the intention of this manuscript is to critically evaluate effects which have a direct impact on the separation efficiency in high temperature liquid chromatography.

2. Theoretical aspects

Although the theoretical aspects regarding the influence of temperature on efficiency, selectivity and retention have been discussed and reviewed extensively, some important and also contradictory aspects will be outlined in this section. The reason is that the chromatographic process is still not completely understood. Subsequently, theoretical models to describe the dependence of analyte retention on temperature are lacking when more than one interaction mechanism is involved.

2.1. Influence of temperature on theoretical plate height

The influence of temperature on the height of a theoretical plate has been a significant point of debate. As is predicted by the van Deemter equation, the dependence of the height equivalent to a theoretical plate (HETP) in dependence on the linear velocity of the mobile phase can be written as:

$$H_u = A + \frac{B}{u} + Cu$$

Although it is often stated that the efficiency always increases at higher eluent temperatures, this hypothesis cannot be supported by the van Deemter equation. Here, the HETP depends on three terms, which are the band broadening due to Eddy diffusion coefficient (A-term), longitudinal diffusion coefficient (B-term) and the resistance to mass transfer coefficient between the mobile and stationary phases (C-term). Physically, it is often assumed that the A-term does not depend on temperature, although Carr states that this is uncertain since high eluent temperatures should improve the laminar flow and lateral mixing of molecules among different flow channels in a column [18]. The remaining B-term and C-term are both temperature dependent. The B-term is directly proportional to the diffusion coefficient while the C-term is inversely proportional to the diffusion coefficient. According to Wilke and Chang

[19], the diffusion coefficient D_M can be written as:

$$D_M \propto \frac{\sqrt{\Psi_2 M_2}}{\eta V_1^{0.6}} T$$

where T is the absolute temperature, M_2 is the molecular weight of the solvent, V_1 is the molar volume of the solute in millilitres and η is the viscosity in centipoise. Ψ_2 is the association factor for the solvent, which is 1 for nonpolar solvents, 1.9 for methanol and 2.6 for water.

It is obvious that the diffusion coefficient is directly proportional to temperature and also inversely proportional to viscosity. This means that by increasing the temperature, the diffusion of analytes in the mobile and stationary phase will be increased. This effect is enhanced because viscosity is also a strong function of temperature. For a liquid, the viscosity decreases with increasing temperature, thereby also enhancing the diffusion of analytes. Therefore it is often assumed that increasing the temperature will lead to an increase of the absolute plate number for a given column. However, Vanhoenacker and Sandra [20] demonstrated that the maximum plate number that can be realised on one particular analytical setup is relatively independent of analysis temperature provided that the mobile phase is adequately preheated to prevent radial temperature gradients. However, the minimum of H in the van Deemter curve shifts to higher linear velocities. Moreover, the steep increase of H as predicted by the van Deemter equation at flow rates higher than the optimum linear velocity is not as pronounced for higher temperatures than will be the case for, e.g. ambient temperature. Therefore, increasing the temperature will improve the efficiency of typical chromatography systems in which $u > u_{opt}$, which has been predicted theoretically [21] and also verified experimentally [22]. This means that one has to be careful when stating that there is an absolute increase in efficiency by increasing the temperature. The increase in efficiency merely results from methods that are not optimised towards maximising the efficiency. In industry, liquid chromatographic methods are usually not run at the optimum linear velocity of the mobile phase and during method development a van Deemter curve is not plotted to find out the minimum plate height at different operating conditions. The net benefit of operating HPLC columns at higher temperatures therefore will be that the operator has not to worry so much about the optimum linear velocity as long as the flow rate is higher than u_{opt} .

Nevertheless, there are some reports which come to different conclusions. One of these studies has been conducted by Yang et al. [23] who noted that the column efficiency is either improved or almost unchanged with increasing temperature in the temperature range between 60 and 120 °C but decreased when temperatures between 120 and 160 °C were applied. This effect was the same for all columns which comprise a Zorbax RX-C8, a PRP-1 (polystyrene divinylbenzene), a Hypersil ODS and a PBD coated zirconium dioxide stationary phase. However, a different result was obtained in a related paper by these authors [24]. In that study, the efficiency of test solutes on a PRP-1 column, a Chromatorex C-18 and a Zorbax RX-C-18 column was recorded at different temperatures ranging from 60 to 140 °C. Here, plate numbers for all analytes always decreased with higher temperatures except for catechol on the PRP-1 column when the temperature was increased from 100 to 140 °C.

This means that there are other factors which are responsible for band broadening and thus a loss in efficiency in high temperature liquid chromatography. An explanation may be found in a review written by Guiochon [25]. In this review, a detailed discussion of the dependence of the HETP on column temperature as a result of radial temperature gradients formed inside the column is given. The evaluation of these effects will be outlined in the following sections. I will continue this discussion in Section 3, where the hardware for

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