



A closer study of peak distortions in supercritical fluid chromatography as generated by the injection



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ABSTRACT

In SFC the sample cannot be dissolved in the mobile phase, so it is often dissolved in pure modifier, or another liquid, sometimes resulting in serious distortions of the eluted peak profiles already at moderately high injection volumes. It is suspected the reasons for these effects are solvent strength mismatch and/or viscosity mismatch. This study presents a systematic and fundamental investigation of the origin of these peak deformations due to the injection solvent effects in SFC, using both systematic experiments and numerical modeling. The first set of experiments proved that the injection volume and the elution strength of the sample solution had a major impact of the shapes of the eluted peaks. Secondly, the sample band elution profile was numerically modeled on a theoretical basis assuming both un-retained and retained co-solvent injection plugs, respectively. These calculations quantitatively confirmed our first set of experiments but also pointed out that there is also an additional significant effect. Third, viscous fingering experiments were performed using viscosity contrast conditions imitating those encountered in SFC. These experiments clearly proved that viscous fingering effects play a significant role. A new method for determination of adsorption isotherms of solvents was also developed, called the "Retention Time Peak Method" (RTPM). The RTPM was used for fast estimation of the adsorption isotherms of the modifier and required using only two experiments.

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1. Introduction

There is a strong trend towards a revival of Supercritical Fluid Chromatography (SFC) with focus on preparative SFC (Prep-SFC) because of its lower environmental impact and shorter run times as compared to preparative liquid chromatography (Prep-LC). This trend was recently summarized by an extensive review written by the now passed away Georges Guiochon and Abhijit Tarafder [1]; in this article was also listed what was identified to be the major "remaining challenges" for the adaptation of SFC as a reliable chromatographic mode. Today, many Prep-LC units have been replaced by Prep-SFC units in the pharmaceutical and fine chemical industrial sector, especially for chiral purifications [2]. More recently the revival of SFC has spilled over to the analytical area driven by strong advances in instrumentation [3,4]. The relatively low viscosity of the mobile phase in SFC as compared to LC makes SFC a prime

candidate to boost the high throughput trend [5] and leading instrument manufacturers have apparently already embarked on this road.

Many of the "remaining challenges" and difficulties with SFC in packed columns resulting in complex behavior [6] are related to the compressibility of the mobile phase in SFC; in a way SFC can be regarded as a "rubber variant of LC" where everything considered as constant in LC is varying in SFC [1]. Altogether, these features of SFC typically result in less reproducibility as compared to LC and poor predictions in scaling up from analytical SFC instruments to preparative SFC instruments. One way of overcoming some of these problems has been to use external devices for measuring the operational conditions in the column [7,8]. Recently, we also employed design of experimental (DoE) approaches to investigate which operational parameters are most important to control for reliable transfer of methods between different system and scaling up for some uncharged compounds [9,10].

In SFC the sample cannot readily be dissolved in the mobile phase, so it is often dissolved in a liquid, or the modifier itself. This can result in solvent strength and viscosity sample solvent–mobile phase mismatch. The mismatch, already at low to moderate high

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sample volumes, will often result in serious distortions of the eluted peak profiles. These combined effects are often simply denoted as “plug effects” [11,12]. It is well-known from LC that injecting the solute in an injection solvent with stronger elution strength as compared to the bulk mobile phase leads to severe and complex band distortions especially at large injection volumes [13–15]. It can be suspected that the underlying reason for these “plug effects” are even more complex in SFC and might also be due to viscous fingering effects. However, except for an experimental study [12], experimental and simulated by Yun et al. [11], or purely theoretical ones [16] there are few studies in SFC aiming at combining experimental evidence and quantifying these phenomena using a modeling approach. In this study we are going to investigate the plug effect utilizing a combined experimental and modeling approach.

There are two main injection principles in SFC [17,18]: (i) the mixed-stream injection mode and (ii) the modifier-stream injection mode, respectively (see Fig. 1). In the first injection mode, the injection is conducted prior to the column after the CO₂ stream and modifier have been mixed (cf. Fig. 1a). The second mode is only used in Prep-SFC and requires that the injection is made in the modifier-stream, which is then mixed with the CO₂ stream (cf. Fig. 1b). Each injection technique has its potential advantages and disadvantages and these were recently evaluated in preparative SFC by Miller and Sebastian [18]. They found that modifier-stream injection was advantageous for many cases, especially for high-volume injections and for solutes having a low retention factor, which were markedly disturbed when performing mixed-stream injections. In a recent publication these problems were realized experimentally and the authors suggested viscous fingering was a principle factor influencing the observed peak distortions, when utilizing the mixed-stream injection mode [11].

When a viscosity mismatch between two fluids is apparent, and one fluid pushes the other, a phenomenon known as viscous fingering (VF) can occur. More particular, in SFC a high viscosity fluid (the ‘plug’) pushes a lower viscosity fluid (the eluent) and the leading interface sharpens. At the same time the trailing interface of the sample band (plug) is penetrated by the lower viscosity mobile phase in a complex manner that resembles fingers [19–22]. In SFC the mobile phase has a lower viscosity than the injection plug, and this viscosity contrast is quite large. However, still no one has investigated and experimentally proved the effects also occur in SFC. Physical evidence of the VF phenomena in liquid chromatography has been obtained by several research groups [23,24]. Shalliker et al. [25,26] used glass columns and a mobile phase which had the same refractive index as the C18 silica; hence, the otherwise opaque column bed became perfectly transparent. The viscosity between the injection plug and the mobile phase could be adjusted and the VF effect visualized either with the aid of colored samples or by

injection of a solvent with a different refractive index to the mobile phase.

The aim of this investigation is to gain a deeper understanding of the major underlying reasons for the peak distortions taking place already at low to moderate sample volumes in SFC. Especially, we aim at investigating the relative impact of the solvent strength and the viscous contrast mismatches, respectively. To investigate this, a three step approach was applied. First, we investigated and compared experimentally modifier- and mixed-stream injections as well as the effect of the sample’s elution strength. Secondly, the sample elution band from mixed stream injections was numerically modeled assuming effects of both un-retained and retained co-solvent, respectively. Finally visualization experiments were conducted using liquid conditions with a viscous contrast between the eluent and sample solution similar to what would be observed in SFC conditions. For estimating the modifier adsorption isotherm without using large injections a new adsorption isotherm acquisition method was developed, the “Retention Time Peak Method” (RTPM).

2. Theory

2.1. Calculating the methanol volume fraction

For simulation of chromatographic experiments, the volumetric fraction of methanol in the eluent was used. However, the instrumentally set conditions need to be verified as they cannot be assumed to be the same as the actual conditions. To calculate this we need to estimate the molar volume of carbon dioxide and methanol. The molar volume of the fluid (V) was calculated according to Kato et al. [27]:

$$V = \frac{M}{\rho}, \quad (1)$$

$$M = x_{\text{CO}_2} M_{\text{CO}_2} + x_{\text{MeOH}} M_{\text{MeOH}}$$

where M is the molecular weight of the fluid, ρ the mass density of the fluid and x is the mole fraction. To estimate the volumetric fraction, the partial molar volume (V_i) needs to be calculated. It could be calculated according to [27]:

$$V_{\text{CO}_2} = V + x_{\text{MeOH}} \frac{\partial V}{\partial x_{\text{CO}_2}}$$

$$V_{\text{MeOH}} = V - x_{\text{CO}_2} \frac{\partial V}{\partial x_{\text{CO}_2}} \quad (2)$$

For a more in depth discussion about Eq. (2) see Eqs. (4) and (5) in Kato et al. [27].

From the calculated molar volume and measured mass flows \dot{m} of carbon dioxide and MeOH it is straight forward to calculate the volumetric fraction of MeOH:

$$v\% \text{MeOH} = \frac{\frac{\dot{m}_{\text{MeOH}}}{M_{\text{MeOH}}} V_{\text{MeOH}}}{\frac{\dot{m}_{\text{MeOH}}}{M_{\text{MeOH}}} V_{\text{MeOH}} + \frac{\dot{m}_{\text{CO}_2}}{M_{\text{CO}_2}} V_{\text{CO}_2}} \times 100 \quad (3)$$

The density of the fluid was estimated using the Kunz and Wagner [28] equation of state as implemented by the National Institute of Standards and Technologies in REFPROP v 9.1. The necessary inputs are the mass fractions of carbon dioxide and methanol, pressure and temperature. The molar fractions were estimated using the measured methanol and total mass flow. $\partial V/\partial x$ were numerically estimated by integrating REFPROP database in CoolProp [29] using a Python 3.x wrapper.

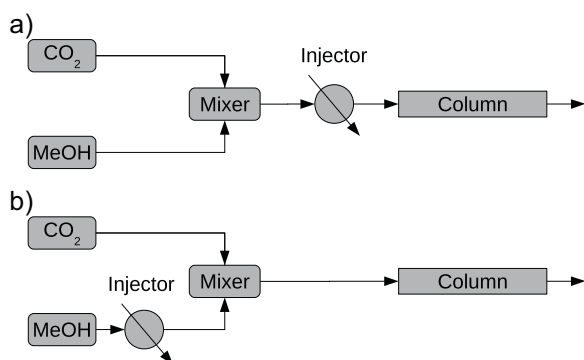


Fig. 1. Schematic figure illustrating system plumbing for (a) mixed stream injection and (b) modifier stream injection.

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