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A scaling rule in Supercritical Fluid Chromatography. I. Theory for isocratic systems

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ABSTRACT

Scaling is regularly done in chromatography either to transfer a successfully designed method of analysis developed in one system to another system, or to scale-up a separation method developed in analytical scale to preparative scale. For liquid chromatography there are well-tested guidelines for scaling, which makes it a routine job. For supercritical fluid chromatography (SFC), on the other hand, neither do we have any well-understood principles behind scaling nor do we know how far the strategies applied in LC could be applicable to SFC. In this article, we have addressed these issues and proposed a rule applicable for scaling isocratic methods between different SFC systems and column dimensions under commonly used operating temperatures and pressures. We have shown that the scale-up and method transfer techniques used in LC can be applied to SFC, provided we ensure that both the original and the target systems in SFC operate at the same average density. The current article will present the theory, discuss the extents of applicability of this rule, and outline its limitations. In an accompanying article implementation of this rule in various practical situations will be presented.

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1. Introduction

Chromatography can provide a separation solution for almost any mixture provided we detect the right combination of stationary and mobile phase chemistry. Determining the right conditions (or method) for separating certain mixtures can be very challenging and may need considerable time, materials and expertise to succeed. Naturally, we try to retain or reuse these methods even when using a different system, for example, a system to run the method faster, or need to change the scale of separation, for example, analytical to preparative scale.

Such transfer of methods is routinely done in chromatography with various motivations. For a transfer within the analytical regime, more commonly called *method-transfer*, the common motivations are to (1) transfer a slower method, previously performed with larger columns and larger particle sizes, to faster analyses employing smaller column dimensions with sub 2 μm particle sizes, (2) transfer methods between different laboratories or sites having the same or different instrumentation to the original method, etc. Method transfer from analytical to preparative separations is more commonly called *scale-up*. Scale-up is an integral part of the design of preparative chromatographic processes. It is often too costly and time consuming to develop a suitable separation method directly in the preparative systems. In many situations, for example, enantioseparation of the Active Pharmaceutical Ingredients (APIs) during the drug discovery phase, the separation specialists routinely do not have sufficient material to develop chromatographic methods directly at the preparative scale. Very commonly, a separation method is first developed in the analytical scale and then *scaled up* for preparative separation. However, in spite of the differences in purpose, *method-transfer* and *scale-up* follow very similar basic principles. Which means any strategy developed for method-transfer can be applied for scaling up as well, and vice-versa. In this article we worked with these basic principles, applicable to both method-transfer and scale-up issues and would mention any transfer of method as *scaling*.

The main application area of the scaling approach we discussed here is for Supercritical Fluid Chromatography or SFC. The advantages of SFC as a separation technique has been discussed in detail in various reviews [1–3]. In summary, because of the application of CO_2 as the principal mobile phase component, separations performed with SFC can be significantly faster, cheaper and environment friendly, hence more sustainable, compared to LC separations. Undoubtedly, preparative separation, a.k.a prep separation, with SFC is fast becoming the norm in many industries, both for chiral and achiral separations [3]. Sample analysis through SFC is also drawing strong interest because of significantly faster separation and orthogonal elution behavior of the analytes, compared

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to LC. Additionally, with the availability of better and more robust instrumentation, there is an increasing interest of using smaller particle size columns for even faster analysis [4]. A crucial component for the success of all these endeavors is to have a technically sound scaling strategy in SFC, which could be conveniently applied in all practical situations.

In spite of this requirement we could not find any suitable scaling strategy reported in the literature specifically for SFC method development. In LC we have model-based optimization strategies [5–8], mostly used in the academia. The model-based approach uses mathematical models to simulate the physical behavior of the chromatographic system. This approach is described in more details in Section 2.1. There are also technically sound rule-based approaches, for example, the so-called L/d_p and $L/d_p{}^2$ rules (discussed in Section 3), successfully used in scaling industrial separations. In SFC the only reported literature on reliable scaling strategies are on model-based approaches [2], which are efficient but not always applicable in practical situations. There are no rule-based scaling approaches or rigorous testing of the LC scaling rules showing their general applicability to SFC systems. Do we need to understand and develop separate scaling methods for SFC or we can apply LC rules directly to SFC? The purpose of this article is to answer these questions and to propose a technically sound rule-based approach for SFC scaling.

The report is organized in the following way. First we present a literature survey of the available scaling strategies. This is followed by a description of the physical mechanism behind the rule-based approaches used in LC. In the succeeding section we discuss the applicability of these rules in SFC in light of the differences between the operations of these two techniques. We show that the main difference between LC and SFC scaling originates from the influence of pressure drop along the column. Geometric scaling rules, for example, the L/d_p rule, lead to differences in column pressure drops between the original and the scaled systems. Although this difference in pressure drops does not affect chromatography in LC, in SFC this leads to differences in solvent densities along the columns, which affects chromatography. To mitigate this difference in density between the original and the scaled column, we propose a method which would enable the LC scaling rules applicable to SFC as well. In the subsequent part of the report we discuss the range of applicability of this method and its limitations. We demonstrate that this approach can be applied for scaling SFC operations between various systems, conditions and column configurations, over a wide range of operating temperatures and pressures.

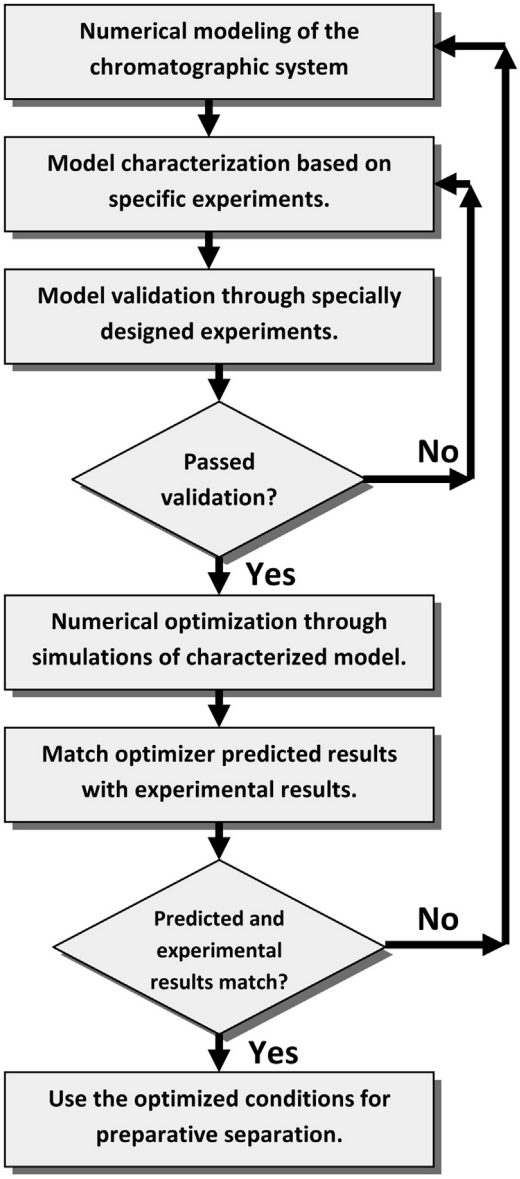

Fig. 1. Flowchart showing the major steps in a simulation-based scale-up strategy.

2. Scaling strategies in chromatography

All the commonly used scaling strategies were developed for and used in the scaling of liquid chromatographic operations. Later, some of them were used in scaling SFC operations. The principles behind the LC scaling strategies are relatively well-understood and documented. Based on a literature survey we could divide the scaling approaches broadly into two categories: (a) model-based approaches, which are mainly practiced within the academic circle, and (b) experimental or rule-based approaches, which are practiced both in the academic labs as well as in industry.

2.1. Model-based approach

The model-based approach takes a holistic view of the task and tries to predict the global optimum performance of the separation at hand. Based on mathematical models of the physico-chemical behavior of a chromatographic system and state-of-the-art computational techniques, simulation-based approach works with a virtual experimental setup. The approach follows the steps shown in Fig. 1. The first step is to have a reliable mathematical model having either an analytical or numerical solution. For smaller molecules the Equilibrium Dispersive (ED) model was found to be sufficient [5,6]. More detailed models, for example, Lump-Kinetic (LK) [9], General Rate (GR) [7,8] and distributed-pore models [10] were found to be more suitable for larger molecules, typically greater than 10kDa. To simulate the results of a particular system, the models are written as computer simulation programs. The program then needs to be "characterized"; by which the values of some "characteristic parameters" of the model are estimated from the data generated by a set of experiments [5,9] performed on a real system. This step makes the simulation program ready as a virtual experimental setup, with which one can rapidly perform experiments to detect optimum operating conditions. Most often an optimization routine is employed, which, through modulating the main operating variables, tries to detect the global optimum conditions of the system. It can be noted that although the simulation-based approach does rely on experimental data performed on analytical systems, it does not limit itself in detecting conditions to *reproduce* the analytical performance in the prep system. With this

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