Preparative chromatography using supercritical fluids

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Publication Date:
2000

Permanent Link:
https://doi.org/10.3929/ethz-a-004082719

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PREPARATIVE CHROMATOGRAPHY USING SUPERCritical fluids

A dissertation submitted to the

SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZURICH

for the degree of

DOCTOR OF TECHNICAL SCIENCES

presented by

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2000
Acknowledgements

At the outset, I would like to express my sincere gratitude to Prof. Marco Mazzotti and Prof. Massimo Morbidelli for their guidance and support during the course of my research. Dr. Werner Dörfler deserves a special acknowledgement since he has shared with me most of the difficult moments that were related to the experimental activity. I am grateful to Mr. Christian Rohrbach, who helped me in the realization of the experimental setup. Many thanks to all my friends at IVUK and at the Chemistry department. The time I spent with them have been pleasant memories which I would always like to cherish. A special word of thanks to Novasep and to the nice people I met there, in particular Félicie Denet and Willy Hauck. I am grateful to Prof. Bala Subramaniam for the interesting scientific discussions we had during his staying in Zürich.

I am profoundly grateful to the all the people who live 400 km away from Zürich, in Italy, who supported me with their care and love in the most difficult moments; in particular I wish to thank my parents and Chiara.

Finally I acknowledge the financial support of the Swiss National Science Foundation.
Curriculum Vitae

Orazio Di Giovanni, born in Cremona, Italy, on December 22nd 1973

Education


October 1997: Politecnico di Milano, Milano, Italy, laurea full marks and honor (100 cum laude /100) in Chemical Engineering (5-year curriculum). Title of the Master dissertation: “Separation of enantiomers through continuous Simulated Moving Bed chromatography in gas phase”.

1988-1992: Liceo Scientifico (58/60) science oriented high school

Experience


Awards/Scholarships


1992-1998: Undergraduate studies supported by Cariplo scholarship

Others

1998 Advanced course in Mass Transfer, Mürren (Switzerland)
1997 Advanced NATO course on Supercritical Fluids, Kemer (Turkey)
August 1995 Stage at the Tamoil refinery in Cremona (Italy)
Abstract

Continuous chromatographic separation processes based on the Simulated Moving Bed (SMB) technology have gained greater and greater importance in the last few years, especially for the separation of high value products (e.g. enantiopure separations). SF-SMB (Simulated Moving Bed using Supercritical Fluids as eluents) represents not only the natural extension of the well-known SMB technique, but allows for further performance optimization. This dissertation focuses both on fundamental and applicative issues.

In fact, on the one hand, the thermodynamics of adsorption under supercritical conditions has been addressed. The adsorption of a single component has been investigated experimentally using an advanced gravimetric technique that allows for a simultaneous measurement of adsorbed amount and fluid phase density. Then, the results have been modeled, analyzed within a thermodynamic framework, and compared with published chromatographic data. The adsorption of a single component under supercritical conditions is not only of scientific interest, but it has direct consequences on the development of SF-SMB technology, since it represents the base for a sound thermodynamic description of adsorption from fluid mixtures.

On the other hand, applicative issues related to the SF-SMB technology have been addressed both experimentally and theoretically. Design criteria for the achievement of the complete separation have been obtained in the frame of the so-called “triangle theory” that has been properly extended to account for the peculiar features of SF-SMBs. For the first time a chiral separation has been carried out in a SF-SMB unit. Complete separation of the two enantiomers has been achieved in both isocratic (constant pressure along the unit) and pressure gradient operating mode (decreasing pressure gradient going from section 1 to 4 of the SMB), but the productivity in the latter case has been almost three times higher, in good agreement with the theoretical prediction.

Finally, the effect of pressure drop in a single SFC column has been analysed and a rigorous approach to calculate thermodynamic parameters from chromatograms obtained in a SFC column with non-negligible pressure drop has been presented.
**Riassunto**

Iprocessi di separazione cromatografica continua basati sulla tecnologia del letto mobile simulato (SMB) hanno acquisito una sempre maggiore importanza negli ultimi anni, specialmente per la separazione di prodotti ad alto valore (per esempio enantiomeri). SF-SMB (SMB con fluidi supercritici come eluenti) rappresenta non solo la naturale estensione della ben nota tecnologia SMB, ma consente un’ulteriore ottimizzazione delle prestazioni. Questa tesi si focalizza sia sugli aspetti fondamentali che su quelli applicativi. In fatti, da un lato, si è affrontata la termodinamica di adsorbimento in condizioni supercritiche. L’adsorbimento di un singolo componente è stata investigata sperimentalmente utilizzando un’avanzata tecnica gravimetrica che consente la misura simultanea di quantità adsorbita e densità della fase fluida. I risultati sono poi stati modellati, analizzati in termini termodinamici e confrontati con dati cromatografici pubblicati. L’adsorbimento di un singolo componente in condizioni supercritiche non è solo di interesse scientifico, ma ha dirette conseguenze sullo sviluppo della tecnologia SF-SMB, in quanto rappresenta la base per una rigorosa descrizione termodinamica dell’adsorbimento di miscele fluide.

D’altra parte, si sono affrontati aspetti applicativi relativi alla tecnologia SF-SMB, sia da un punto di vista sperimentale che teorico. I criteri di progetto per il raggiungimento delle condizioni di completa separazione sono stati ottenuti nell’ambito della cosiddetta “teoria del triangolo” che è stata opportunamente estesa per tener conto delle caratteristiche peculiari dell’SF-SMB. Per la prima volta una separazione chirale è stata condotta in un’unita’ SF-SMB. E’ stata conseguita la separazione completa dei due enantiomeri sia nel modo operativo isocratico (pressione costante nell’impianto) e nel modo a gradiente di pressione (gradiente di pressione decrescente dalla sezione 1 alla 4), ma la produttività nel secondo caso è stata quasi 3 volte superiore, in buon accordo con le previsioni teoriche.

Infine, l’effetto delle perdite di carico in una singola colonna cromatografica con eluenti supercritici è stato analizzato ed è stato proposto un approccio rigoroso per il calcolo dei parametri termodinamici da cromatogrammi ottenuti in una colonna con eluenti supercritici con perdite di carico non trascurabili.
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CHAPTER 1

Introduction

This first Chapter gives an overview of the state of the art about preparative chromatography in general (section 1.1) and about the combination of chromatography and supercritical fluids in particular (section 1.2 and 1.3). The goal is to make the reader familiar with the concepts developed in the following chapters and to give the motivation for this research project. The objectives of this work are then discussed in section 1.4 where also the structure of this dissertation is presented.

1.1 Large scale chromatography

Over the last few years preparative chromatography has been increasing its importance as a separation and purification process in the pharmaceutical, agrochemical and food industries wherever classical techniques, such as distillation, are not feasible. Most applications involve batch preparative chromatography; however a remarkable breakthrough has been
achieved by the development of large scale continuous chromatography, which allows significant advantages in terms of process performance to be achieved.

A SMB (Simulated Moving Bed) is a continuous unit based on the simulation of the equivalent True Moving Bed (TMB) unit illustrated in Fig 1.1. This is divided into 4 sections, each consisting of a counter current adsorption column which plays a specific role in the separation. Let us consider a feed mixture consisting of a more retained species (A) and a less retained species (B) dissolved in the eluent.

In sections 2 and 3, according to the scheme reported in Fig 1.1, the separation is performed and A is adsorbed while B is eluted. In section 1 A is desorbed and therefore the solid is regenerated, while in section 4 B is adsorbed and therefore the eluent is cleaned and can be recycled to section 1. In this way, A is collected in the extract and B in the raffinate.
Unfortunately, in order to realize such a process the motion of the solid adsorbent is needed and this cannot be accomplished in practice without a considerable backmixing, which strongly reduces the efficiency of the process. This problem can be overcome by using a system consisting of several fixed-bed columns arranged as represented in Fig 1.2, where the countercurrent flow of the solid and the fluid is simulated by periodically changing the position of the inlets and the outlets in the direction of the fluid flow. In this way the solid must not be moved: the concentration profiles migrate inside the columns but the points of injection and withdrawal follow them allowing the generation of a cyclic steady state, where this migration of fronts is repeated each time in the same way.

![Fig. 1.2: Scheme of a Simulated Moving Bed unit. Column layout: 2-2-2-2](image)

This process, the Simulated Moving Bed (SMB), was invented in the early 1960s by UOP and is known as SORBEX technology (cf. (Broughton, 1961)). Initially it was applied to large-scale separations of hydrocarbons, such as p-xylene from C8 aromatic mixtures (PAREX process) or linear paraffins from branched hydrocarbons (MOLEX process), and to the separation of fructose from glucose (SAREX process). Commercial applications
operate in the liquid phase, but also vapor phase operation has been demonstrated feasible by some pilot scale experiments ((Storti, 1992), (Juza, 1998)). More recently, the availability of new stationary phases, in particular chiral stationary phases for the resolution of racemates, has made it possible to down-scale the SMB technology to fine chemical separations ( (Nicoud, 1999a), (Nicoud, 1999b), (Juza, 2000)).

In fact, most available ways to prepare pure enantiomers are very expensive and time-consuming. Preparative chromatography is a rather good solution to this problem: analytical chromatography is widely adopted to characterize the composition of mixtures of products during the synthesis. In most cases preparative separations can be directly developed using the same method (same stationary phase and mobile phase) adopted for analytical purposes and the scale-up can be realized successfully in a short time. This is a crucial advantage in the Pharmaceutical Industry, where due to the heavy competition the time-to-market can be a key parameter for the success of a new product. However, several researchers have demonstrated that, when compared to the classical batch preparative chromatography, most often SMB units exhibit better performances in terms of solvent consumption and productivity per unit mass of stationary phase (Francotte, 1997). In fact, in SMB units the components are required to be pure only at the positions where extract and raffinate are collected. Thus, the concentration profiles of the components to be separated are allowed to overlap, while in batch preparative chromatography they must be completely resolved. This allows to operate at higher concentrations and therefore with a lower amount of eluent and stationary phase per unit mass of pure product.

Technological issues of liquid phase SMBs have been satisfactorily dealt with using devices typical of HPLC chromatography. Criteria for the optimal design of such units have been developed, which allow to account for the important nonlinear competitive character of the adsorption equilibria involved (cf. (Mazzotti, 1997b) and chapter 4 of this dissertation). All these activities have generated a lot of scientific interest in the SMB technology, indicated by the increasing number of research groups in the world which are now involved with it. The first industrial scale plant (10 t/y of racemic feed) for the separation of the enantiomers of a chiral compound has been put into production at the beginning of 1998 in Belgium at UCB (cf. (Cavoy, 1997) for details about this application). However, we believe that this technology has some further potential which has not been exploited
yet. The starting ideas come again from analytical chromatography and involve the application of SMBs to supercritical fluid chromatography (SFC).

1.2 Supercritical fluid chromatography (SFC)

Supercritical fluid chromatography (SFC) is today a widely used, rapid and efficient analytical tool, since it is complementary to both gas (GC) and liquid chromatography (HPLC). In fact, SFC can be applied to thermally labile and non volatile compounds, where GC cannot be used, and it has a higher efficiency and compatibility with numerous detectors as compared to HPLC. Nowadays, equipment for SFC are widely available from several suppliers worldwide ((Berger, 1990a), (Perrut, 1994)). However, in the last few years, SFC has increased its importance also as a preparative method since it allows for negligible organic solvent disposal and remarkable process performance. Table 1.1 reports the main contributions in this area in which the nonlinear adsorption equilibria have been determined. Other applications in which no detailed thermodynamic analysis has been carried out are reported simply as citations in the text. It is worth noting that in all these works the supercritical fluid used is carbon dioxide, which critical parameters are: temperature $T_c=31^\circ\text{C}$, pressure $P_c=73$ bar and density $\rho_c=470$ kg/m$^3$. This allows operation near ambient temperature and under reasonable pressure, which is in general between 100 and 200 bar (cf. Table 1.1). Furthermore, carbon dioxide is non-toxic, non-flammable and has a benign character. This is very important for agrochemical, pharmaceutical and cosmetic industries, where process steps must be carried out under mild conditions to avoid thermal degradation and without the use of hazardous chemicals. However, until now, most of the applications are related to removal of organic pollutants using activated carbon as adsorbent ((Picht, 1982), (Kander, 1983), (MacHugh, 1986), (Madras, 1993), (Macnaughton, 1995), (Srinivasan M. P., 1990), (Tan, 1990), (Harikrishnam, 1998), (Shojibara H., 1995)). The pollutant may be present in small percentage in either drinking or residual water or in gas streams that need to be purified. The use of supercritical carbon dioxide has shown to be an efficient method for the regeneration of these adsorbents. The same chromatographic process, i.e. the so-called adsorption-desorption mode, has been applied to deterpenation of citrus oil on silica (Subra, 1998). More recently preparative SFC has been applied to separation of mixtures of aromatics ((Iwai, 1994), (Cross, 1998))
and fatty acids (Perrut, 1983) in elution mode. There is also an example where pressure swing adsorption with supercritical carbon dioxide is used for fractionation of citrus oil (Sato, 1998).

The advantages of SFC trace back to the more general features of supercritical fluids, which exhibit properties that are intermediate between those of the liquid and the gas phase. In fact supercritical fluids possess liquid-like density and gas-like viscosity, whereas diffusivity is intermediate. Therefore, since solubility is correlated to density, solubility in supercritical fluids is rather similar to that exhibited in liquid solvents, while the transport properties and pressure drop are improved when compared to liquids. Even more interestingly, these properties change rather sharply for changes of temperature and pressure near the critical values. Therefore the solubility in supercritical fluids can be rather easily tuned by changing density, through changes of pressure. These features make supercritical fluids tunable solvents with a continuous transition between good solvents under supercritical conditions and poor solvents in the state of a compressed gas. However, the solubility of polar compounds in supercritical carbon dioxide is not sufficient for many applications. This serious drawback may often be overcome by adding one or more cosolvents to increase the solvent power of the fluid (Brennecke, 1989).
Let us now consider the specific characteristics of supercritical fluid chromatography. As already mentioned, in the supercritical region the solvating power of the fluid is highly dependent on temperature and pressure, and so is the affinity of a given solute for the supercritical fluid phase itself. The affinity of the same solute for a given stationary phase is also a function of temperature. The coupling of these two effects yields a temperature and pressure dependence of the partition constant of a given solute between the stationary phase and the supercritical solvent at equilibrium (Perrut, 1994). In linear chromatography the partition constant, i.e., the ratio between the adsorbed and the fluid phase concentrations of the solute, is given by the Henry constant, $H$. The larger the Henry constant, the larger the retention time in a chromatographic column, which depends on temperature and pressure through $H$. This effect may be accounted for by the following simple empirical equation which relates the Henry constant of the solute to the density of the supercritical solvent, $\rho$, which in turn depends upon temperature and pressure (van Wasen, 1975):

$$H = H^0 \left(\frac{\rho}{\rho^0}\right)^b$$

where $H$ and $H^0$ are the Henry constants of component $i$ at the operating and reference densities $\rho$ and $\rho^0$, respectively, and $b$ is an empirical coefficient, depending on $T$ and on the chromatographic system, i.e. solvent and stationary phase. Typical values of $b$ are in the range 1 to 5. For example $b$ equals 2.73 in the case of the most retained enantiomer of tetralol on a ChiralOD SFC column using carbon dioxide modified with 5.4 % (w/w) of Ethanol as mobile phase at 40 °C (cf. Chapter 5). This implies that the retention time of tetralol on this stationary phase doubles when pressure is decreased from 250 bar (corresponding to $\rho=885$ kg/m$^3$) to 100 bar ($\rho=700$ kg/m$^3$). If the elution of phenanthrene using neat carbon dioxide on Lichrospher 100 RP-18 at 65 °C is considered (cf. Chapter 6), $b$ equals 4.5. Therefore the same decrease in pressure (from 250 to 100 bar) implies a decrease in density from 763 kg/m$^3$ to 265 kg/m$^3$ and a change in the Henry constant of more than 100. It is worth noting that large values of the Henry constant imply small elution strength of the mobile phase and vice versa; in fact the larger the Henry constant of the solute, the longer the time and the bigger the amount of solvent needed to elute a given amount of the solute itself.
The possibility to tune the solvent elution strength by changing the pressure is a peculiar feature of SFC and it has many practical consequences. At an analytical scale, it is exploited to generate elution gradients during the sample elution, in analogy with the solvent gradients in HPLC. At a preparative scale, the total pressure represents a further degree of freedom in the process design and it needs to be optimized like the choice of the solvent in HPLC. However the same supercritical solvent at different pressures exhibits a rather wide range of properties, while the total pressure has a negligible effect on the elution properties of a liquid solvent. Therefore different separations that, if carried out in liquid phase, required different solvents can be realized in sc-CO₂ at different pressure levels. Furthermore, the tunability of the solvent properties appears very attractive for SMBs as it will be discussed in the next section.

### 1.3 Supercritical fluid simulated moving bed (SF-SMB)

The combination of the Simulated Moving Bed and the supercritical fluid technologies, through the use of a supercritical eluent, is referred to as Supercritical Fluid Simulated Moving Bed (SF-SMB). The well known advantages of SFC, namely easy separation of products and solvent and full compatibility of the most common solvent (i.e. CO₂) with product bound to be used by humans, can be maintained also at the SMB scale. Moreover, the SMB performance can be improved by taking advantage of the tunability of physical properties of near critical solvents (Clavier, 1996). As discussed in the previous section, it is found that at higher density the solute is eluted faster, according to Eq (1.1). Recalling the different function of each section in the TMB unit described above, it is clear that a decreasing density gradient (i.e. a decreasing gradient of elution strength) results in principle in better performance as compared to a constant density profile, corresponding to a constant elution strength in the four sections of the unit. This can be readily understood by noting that in the former case the elution strength is maximum in section 1, where the more retained component must be eluted, and it is minimum in section 4, where the less retained component must be adsorbed by the stationary phase.

This concept has been illustrated experimentally by inducing the density gradient through a proper pressure gradient. Since pressure drop in each column is negligible in this context, the different pressure values in each section of the unit has been realized using a sys-
tem of back pressure valves placed between each pair of columns. In particular, the improvement of SMB performance when a pressure gradient is applied (pressure gradient mode) in comparison to operation under uniform pressure (isocratic mode) has been demonstrated experimentally for the separation of two fatty ethyl esters (GLA, i.e. γ-linoelic ethyl ester and DHA, i.e. docosahexaenoic ethyl ester) on C18 bounded silica (Clavier, 1996).

Most of the separation processes of industrial interest involve heavy and polar organic molecules that show a low solubility in pure carbon dioxide and cannot be eluted on standard stationary phases, e.g. the silica based ones. To overcome this problem, small amounts of an organic solvent (modifier) are added to the pure CO₂ (cf. section 1.2). The modifier is believed to act both in the fluid phase (by increasing the solubility of the solute) and in the stationary phase (by deactivating strongly polar groups, e.g. silanols). The net effect is a decrease of the retention time when increasing the modifier concentration. From these considerations it appears that also in the case of SF-SMBs, eluents are likely to contain a modifier. Therefore the choice of the modifier concentration increases the degrees of freedom of the process and must be considered while designing the operating conditions of the separation.

1.4 Objectives of the work

The aim of this research project is to foster the application of supercritical fluid chromatography (SFC) to production scale separations in industry, particularly through the Simulated Moving Bed technology using a supercritical eluent (SF-SMB). The application of this promising technology, in particular in pharmaceutical, agrochemical and food industries, is still limited due to the lack of a satisfactory understanding of the fundamental phenomena involved, such as the adsorption thermodynamics of supercritical mixtures, and of a thorough assessment of the strengths and potentials of the technique from the viewpoint of performance and practical implementation.

The investigation has therefore addressed both fundamental and applicative issues. On the one hand, in fact, the effect of the density level on the retention times in a chromatographic column (which has been described briefly in section 1.2 and is exploited in the SF-SMB pressure gradient operating mode) reflects the effect of the density value on the ad-
Introduction

sorption isotherm of the solute. Until now, this issue has been addressed in a rather empirical way (cf. e.g. (Kikic, 1996)). A proper understanding of this phenomenon requires a sound thermodynamic description of the system that takes into account both the competition of the supercritical solvent and the non-idealities in the fluid and adsorbed phase. The first step in this direction is the measurement and modeling of the solvent adsorption isotherm. Chapter 2 and 3 deal with this subject. In particular, in Chapter 2, the experimental technique is described in detail and the adsorption isotherms of carbon dioxide on silica gel are presented and modeled according to the different approaches present in literature. In Chapter 3 the experimental procedure has been applied to different pairs solvent/adsorbent, thus allowing a comparison of systems with different physico-chemical properties.

The second part of the dissertation is focused on more applicative issues related to SFC and SF-SMB technology. In Chapter 4 design criteria for a SF-SMB unit operating both under linear and nonlinear adsorption equilibria are derived in the frame of the so-called triangle theory. These findings are of basic importance both for a proper optimization of SF-SMB performance and for the design and interpretation of SF-SMB experiments, which are presented in Chapter 5. The experiments have been carried out using a SF-SMB pilot plant at NOVASEP (Nancy, France), which has cooperated with us in this part of the project. For the first time, a chiral separation has been realized in a SF-SMB unit. The experimental results have shown a remarkable improvement of the productivity in the pressure gradient operating mode when comparing it with the isocratic mode. Finally, Chapter 6, addresses the issue of pressure drop in a single chromatographic column. In the last chapter of this dissertation, the main results of this work are briefly summarized and the main objectives for a future work are indicated.
The knowledge of accurate high-pressure adsorption equilibrium data is of great practical importance for several classes of industrial processes (including adsorption based separations, regeneration of adsorbents in purification processes and heterogeneous catalysis). The aim of this and of the following chapter is to address this topic with special attention toward chromatographic systems. However the approach adopted here is rather fundamental and results of this investigation may be applied to all the processes involving the adsorption under supercritical conditions.

SFC systems are in general quite complex since they usually involve at least four components (solvent, modifier, two solutes to be separated) in contact with the adsorbent. A rigorous thermodynamic approach must take into account:

1) nonideality of the fluid phase
2) nonideality of the adsorbed phase
3) competition of the different components in occupying the adsorption sites.
Adsorption of supercritical CO₂ on silica gel

The thermodynamics of complex supercritical fluid mixtures has attracted the interest of many researchers in the last 10 years. In order to give a sound thermodynamic description of the adsorption of mixtures, the information about the fluid phase behavior should then be combined with the adsorption isotherms of each single component constituting the mixture (cf. Real Adsorption Solution Theory (Talu, 1986)). In this perspective, the knowledge of the solvent isotherm is of fundamental importance.

The adsorption of a single gas at high pressure and under supercritical conditions has been the objective of different investigations in the last decades. The main contributions are listed in Table 2.1 and, for each of them, the system (fluid and solid), the range of operating conditions and the experimental method are reported.

<table>
<thead>
<tr>
<th>reference</th>
<th>fluid</th>
<th>adsorbent</th>
<th>T [K]</th>
<th>P [bar]</th>
<th>method</th>
</tr>
</thead>
<tbody>
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<td>(Moffat, 1955)</td>
<td>CH₄</td>
<td>AC</td>
<td>298</td>
<td>1-1000</td>
<td>volumetric</td>
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<tr>
<td>(Michels, 1961)</td>
<td>N₂</td>
<td>Allumina</td>
<td>265.5-373</td>
<td>1-3000</td>
<td>piezometric</td>
</tr>
<tr>
<td>(Menon, 1965)</td>
<td>CO</td>
<td>Allumina</td>
<td>273-323</td>
<td>1-2000</td>
<td>piezometric</td>
</tr>
<tr>
<td>(Hori, 1970)</td>
<td>CH₄</td>
<td>silica beads (Porasil)</td>
<td>181-304.5</td>
<td>5-120</td>
<td>chromatographic</td>
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<td>(Ozawa, 1976)</td>
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<td>1-170</td>
<td>volumetric</td>
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<tr>
<td>(Specovius, 1980)</td>
<td>C₂H₄</td>
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<td>263-323</td>
<td>1-120</td>
<td>gravimetric</td>
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<tr>
<td>(Strubinger, 1989)</td>
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<td>silica C18</td>
<td>303-373</td>
<td>5-200</td>
<td>chromatographic</td>
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<td>AC</td>
<td>298</td>
<td>1-6500</td>
<td>volumetric</td>
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<td>(Staudt, 1993)</td>
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<td>298</td>
<td>1-160</td>
<td>gravimetric</td>
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<td>1-5000</td>
<td>volumetric</td>
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<tr>
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<td>304-328</td>
<td>1-180</td>
<td>volumetric</td>
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<tr>
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<td>AC</td>
<td>284-314</td>
<td>1-160</td>
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<td>(Salem, 1998)</td>
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<td>AC</td>
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<td>1-160</td>
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<tr>
<td>(Zhou, 2000)</td>
<td>CH₄</td>
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<td>258-318</td>
<td>1-200</td>
<td>gravimetric</td>
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<th>adsorbent</th>
<th>T [K]</th>
<th>P [bar]</th>
<th>method</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Zhou, 2000)</td>
<td>CH₄</td>
<td>AC</td>
<td>233-333</td>
<td>1-100</td>
<td>volumetric</td>
</tr>
</tbody>
</table>

**TABLE. 2.1: State of the art**

Since the pioneering work of Michels et al. (Michels, 1961), all the authors have been aware that the only measurable property is the adsorption excess, $n^{ex}$. For adsorption on a flat surface $A$ this is defined in terms of the density profile as:
Adsorption of supercritical CO2 on silica gel

\[ n^{ex} = A \int_{0}^{\infty} (\rho(z) - \rho) \, dz \]  
\[ (2.1) \]

where \( \rho(z) \) is the density of the fluid at a distance \( z \) from the surface of the solid and \( \rho \) is the fluid bulk density. When considering the adsorbed phase as a homogeneous phase of specific volume per gram of adsorbent \( V_A \) and average density \( \rho_A \), the excess amount adsorbed is related to the absolute amount adsorbed through the following relationship:

\[ n^{ex} = n^{abs} - \rho V_A = V_A (\rho_A - \rho) \]  
\[ (2.2) \]

At high density the second term, \( \rho V_A \), becomes of the same order of magnitude as the first one and the excess isotherm exhibits a maximum. Although the right hand side of Eqs (2.1) and (2.2) are based on different physical descriptions of the systems, this difference has no effect on the measurement of \( n^{ex} \), but only on the way adsorption is modeled (see section 2.3 below).

All the methods proposed for the evaluation of the absolute adsorption require assumptions about the nature of the adsorbed phase. Hory and Kobayashi suggested a chromatographic method for the measurement of the absolute adsorption based on the “Hypothetical Perfect Gas” perturbation technique (Masukawa, 1968), but with additional corrections to take into account the specific features of high pressure adsorption (Hori, 1971). All the other methods yield excess adsorption quantities and most of the attempts to derive absolute quantities are based on rather arbitrary assumptions like the one of constant adsorbed phase density or constant adsorbed phase volume. Many authors, based on the observation that the high density branch of the isotherm decreased almost linearly with density, have assumed that the saturation of the adsorbed phase has been reached and used the slope of this straight line to estimate the adsorbed phase volume (Michels, 1961). This value is then applied also to the low density branch and to the region where the maximum occurs. However, Findenegg et al. have shown that the density profile at the wall changes quite dramatically, especially close to the critical point and the correlation length becomes long-ranged when the critical temperature is approached (Blümel, 1985). Other authors, dealing with microporous adsorbents, assume that the adsorbed phase volume coincides...
with the pore volume (Salem, 1998). In the following, the data presented and the related thermodynamic analysis are based on directly measuring excess properties with no assumptions on the nature of the adsorbed phase.

Most of the measurements reported in literature have been carried out using either a volumetric or a gravimetric method. The two main sources of errors using these two methods are the estimation of the fluid phase density and of the adsorbent volume.

The knowledge of the fluid phase density is of key importance, since it appears in the mass balance (volumetric method) and in the buoyancy correction (gravimetric method). In general the fluid phase density has been calculated from the temperature and pressure measurements using a proper equation of state. However, it is well known how the prediction of the density value from the pressure and temperature readouts is strongly affected by the uncertainty of these measurements, especially close to the critical point (Levelt Sengers, 1993). Furthermore, in most of the experimental set-ups reported, the temperature sensor was placed on the wall of the measuring cell; therefore the measured temperature could be different from the fluid phase temperature, especially when the temperature control was achieved through a thermostating jacket. Among the works listed in Table 2.1, the only experimental set-up provided with an in situ density measurement is the one used by Malbrunot et al., in which the density is measured using a capacitance cell. The present work is, to our knowledge, the first one in which the high pressure adsorption data have been obtained with a gravimetric method and with an in situ determination of the density, as explained in details in the following.

The second source of errors is the estimation of the volume of the adsorbed material that is usually obtained by carrying out a blank run using helium, which is considered non adsorbable. However, Malbrunot et al. have shown that, especially at low temperature, helium adsorbs to a certain extent, thus leading to a significant underestimation of the adsorbed amount (Malbrunot, 1997). They showed that the adsorbent volume increases continuously when the operating temperature ranges from room temperature to 400°C. In the present work, the adsorbent volume has been measured using helium at 200 °C in order to minimize this problem and to avoid, at the same time, the degradation of the silica surface that occur at very high temperatures.

In this work, adsorption isotherms of pure CO₂ on silica have been measured using for the first time a gravimetric method. It is, to our knowledge, also the first time that adsorption
data of the system CO2/silica have been measured in such a wide range of pressure and temperature values and with a high precision, thanks to the direct measurement of the fluid phase density.

## 2.1 Experimental procedure

The carbon dioxide isotherm measurements have been carried out using a Rubotherm magnetic suspension balance. The instrument has already been used for high pressure adsorption measurements of several gases on microporous adsorbents and for the sorption of CO2 in swellable polymers, but it is the first time that adsorption isotherms of CO2 on silica gel have been measured using this technique at a pressure higher than 100 bar.

The basket containing the adsorbent sample is suspended at a permanent magnet and placed in the adsorption cell, which is kept at the established pressure and temperature. The permanent magnet is suspended, thanks to an electromagnet placed outside the cell, i.e. at ambient conditions. The latter is then connected to an analytical balance that receives the weight values measured inside the cell and is transmitted through the magnetic coupling. A detailed description of this instrument is reported elsewhere (Weireld, 1999).

In the experimental set-up used in the present work, a titanium sinker of calibrated volume is also present that allows for the simultaneous density estimation. Thus summarizing there are three main elements inside the measuring cell that can be weighed (see Fig. 2.1): the permanent magnet, the basket and the sinker.

These three elements are connected by two coupling systems (CS1 and CS2) and the permanent magnet can be suspended at three different heights by modulating the current of the electromagnet. In this way it is possible to measure the three elements separately.

In the measuring position 0 (MP0) only the magnet is suspended and weighed and the two coupling system are set down on their supports. In the measuring position 1 (MP1) the magnet is in a slightly higher suspension state and also the basket is lifted thanks to the first coupling system (CS1), while the titanium sinker still lays on its support. In the measuring position 2 (MP2) also the sinker is lifted and the balance provides the total mass of the system. The difference between the weight measured at MP2 and at MP1 gives the mass of the sinker:
FIG. 2.1: Operating principle of the four positions magnetic suspension balance

\[ MP2 - MP1 = m_{\text{sinker}} = m^{0}_{\text{sinker}} - \rho V_{\text{sinker}} \]  

(2.3)

where \( m^{0}_{\text{sinker}} \) is the mass of the sinker under vacuum, \( V_{\text{sinker}} \) is its volume, and buoyancy is accounted for. The volume \( V_{\text{sinker}} \) is determined before starting the experiment by measuring its mass in two media of known density (three times distilled water and air of measured temperature, pressure and humidity). Since \( m^{0}_{\text{sinker}} \) is easily measured under vacuum as \( MP2^{0} - MP1^{0} \), the fluid phase density can be determined from Eq (2.3).

In the following we shall consider only the signal in MP1 that we indicate with \( \Omega \) and the subscript will refer to the different experimental conditions, i.e. 0, 1 and 2 refer to measurements under vacuum, with He and with CO\(_2\), respectively. A known amount of silica gel (Kieselgel 60, Merck, batch number 1.07734.1000) is first dried in an oven at 200 °C for 3 hours and then placed in the adsorption cell. The cell is then connected to a vacuum line and the temperature is maintained at 100°C, while a weight decrease is observed. Af-
After about 4 hours, when the curve weight vs. time flattens (the decrease in MP1 is less than $1 \times 10^{-4}$ g/h), the degassing procedure is stopped. The balance signal coincides, at this stage, with the weight of the adsorbent plus the metal basket and other metal parts, i.e. $m_0$:

$$\Omega_0 = m_0$$ (2.4)

The cell is then maintained at 200 °C and filled with helium at 200 bar, which can be assumed to be non adsorbable if the temperature is high enough. The balance signal at this stage corresponds to:

$$\Omega_1 = m_0 - \rho_{He} V_0$$ (2.5)

where $V_0$ is the volume of the adsorbent particles plus the metal parts of the basket, whose overall mass is $m_0$. Since the density is calculated from the value measured in MP2, the volume $V_0$ is obtained by combining Eqs (2.4) and (2.5).

The system is evacuated and then CO$_2$ is fed to the cell at different pressures. The balance signal is now:

$$\Omega_2 = m_0 + m_A - \rho (V_0 + m_{ads} V_A)$$ (2.6)

where $m_A$ is the mass of the CO$_2$ adsorbed, and $m_{ads}$ is the mass of adsorbent, which is measured after evacuation. The CO$_2$ density $\rho$ is measured independently as discussed above.

The excess adsorbed amount of CO$_2$ on silica can finally be determined by using Eq (2.6) together with Eqs (2.4) and (2.5):

$$n = m_A - \rho m_{ads} V_A = \Omega_2 - \Omega_0 - \frac{\rho}{\rho_{He}} (\Omega_0 - \Omega_1)$$ (2.7)

From Eq (2.7) the excess amount mass adsorbed per unit mass of adsorbent is obtained as:

$$n^{ex} = \frac{n}{m_{ads}}$$ (2.8)
Let us now focus on the measurement accuracy. The mass is measured by the balance with an absolute accuracy of 0.01 mg. However, two kinds of noises could be observed and the accuracy has been limited to 0.1 mg. In fact, on the one hand, high frequency vibrations of the floor of the lab could be observed that lead to weight oscillations of about 0.05 mg (with typical load in MPI of 10 g). On the other hand, the temperature in the cell oscillates between day and night of 0.1 K thus leading, for our system, to an overall uncertainty always lower than 0.1 mg. The measurement of the adsorbent volume has been repeated three times. The average value has been used in the calculations and the difference between the minimum and maximum value obtained has been assumed as the error on the measurement. The volume of the titanium sinker is known with an accuracy of 0.05% and the mass of the adsorbent has an absolute accuracy of 0.01 mg. Combining the different sources of errors, the error on the estimation of the specific excess amount adsorbed is:

\[
\left| \Delta n^{ex} \right| = \frac{|\Delta n|}{m_{ads}} + \frac{n}{m_{ads}} \cdot \frac{\Delta m_{ads}}{m_{ads}}
\]

(2.9)

Since the main source of error is the buoyancy correction, the error increases almost linearly with the density and its main contribution is the error that derives from the estimation of the adsorbent volume. In Fig. 2.2 the error as a function of density is reported for the experiment at 312 K. The maximum error is around 2% and no variation with the temperature could be observed, when points at the same density were compared.

### 2.2 Results and discussion

Several measurements have been repeated in both adsorption and desorption mode. Good reproducibility and no hysteresis have been observed. The measurements have been performed at one subcritical and nine supercritical temperature values (CO2 critical temperature is 304.1 K). The excess adsorbed amounts per unit mass of the adsorbent, i.e. \( n^{ex} \), are reported as a function of density in the Appendix, where also the corresponding pressure calculated using the Span and Wagner equation of state is indicated (Span, 1996). At a temperature lower than the critical one, at the saturation pressure, which is about 58 bar
at 294 K, liquid is formed and the adsorption loading increases indefinitely. Therefore the maximum experimental pressure has been maintained below this value and the CO₂ loading monotonically increases in this pressure range. In the following we will focus only on the supercritical isotherms and, for the sake of clarity, the plots and tables will contain only eight of them (the isotherm at 330 K is never reported). In Fig. 2.3 these eight isotherms are plotted as a function of density. All the supercritical isotherms exhibit a maximum, since they represent excess quantities and no crossover is observed, in agreement with previous works (Strubinger, 1991),(Specovius, 1980).

However, when the data are plotted as a function of pressure as in Fig. 2.4, all the isotherms intersect beyond the maximum. Adsorption maxima occur at higher pressure when the temperature increases and the adsorption loading corresponding to the maximum decreases with temperature.

These conclusions are consistent with similar adsorption data obtained with a volumetric method on LiChroSpher Si100 (Bamberger, 1996). The latter has very similar properties.
20 Adsorption of supercritical CO2 on silica gel

FIG. 2.3: Excess amount of carbon dioxide on silica gel as a function of the fluid phase density.

to the one used in the present work. The comparison with these data shows also a fairly
good quantitative agreement, both in the loaded amounts as well as in the pressures at
which the maxima occur.

This observation suggests some similarities to what happens for solubility data, where the
‘crossover effect’ disappears when the data are plotted as a function of density, thus con¬
fiming once again that the density is the meaningful variable to represent high pressure
thermodynamic data. Moreover in Fig. 2.3 the adsorption maxima occur at similar density
values. Similar observations have been reported for data obtained on a similar system us¬
ing a mass spectrometric tracer pulse chromatographic technique (Strubinger, 1991).

2.3 Modeling

Two different approaches can be followed when modeling high pressure adsorption data.
On the one hand, the experimental excess adsorption data can be converted into absolute
quantities and then described using conventional adsorption models. On the other hand, specific theories and models have been developed over the last few years to predict the density profile at the wall of the adsorbent (Aranovich, 1996), (Subramaniam, 1995). If the density profile is established, then the integration of Eq (2.1) leads to the excess amount that can be directly compared with the experimental data.

Let us now consider the first approach. The two most common assumptions are either that the density of the adsorbed phase is constant ($\rho_A$ = const) or that its volume is constant ($V_A$ = const), leading either to:

$$n^e = n^{abs} \left( 1 - \frac{\rho}{\rho_A} \right)$$  \hspace{1cm} (2.10)

or to:

$$n^e = n^{abs} - V_A \rho$$  \hspace{1cm} (2.11)
respectively. Here $n_{\text{abs}}$ is given by a model of the absolute adsorbed amount and $\rho_A$ and $V_A$ represent in each case an additional fitting parameter. Though aware of the oversimplification of this approach, we have applied it to the experimental data above using both a Langmuir model (Fig. 2.5) and a B.E.T. model (Fig. 2.6). The Langmuir model is given by:

$$n_{\text{abs}} = \frac{n_m b \rho}{1 + b \rho}$$

(2.12)

where $n_m$ is the monolayer capacity that should be temperature independent and $b$ should depend on temperature according to the van’t Hoff law:

$$b = b_0 \exp\left(\frac{\Delta H_0}{RT}\right)$$

(2.13)

The results of the fitting are reported in Table 2.2 for the temperature dependent parameters, while $n_m$ is 0.55 g/g.

A plot of $\ln(b)$ vs. $1/T$ gives a straight line with a correlation coefficient equal to 0.996. The heat of sorption, $\Delta H_0$, calculated from this diagram is equal to about 71 J/g that is of the same order of magnitude of the specific excess enthalpy $\Delta h_{\text{ex}}^s$, defined in section 2.4. The density of the adsorbed phase $\rho_A$ decreases with the temperature. The fitting has

<table>
<thead>
<tr>
<th>$T$ [K]</th>
<th>Langmuir</th>
<th>B.E.T.</th>
<th>Lattice model</th>
<th>SLD model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$b$</td>
<td>$\rho_{\text{ads}}$ [g/L]</td>
<td>$C$</td>
<td>$\rho_{\text{ads}}$ [g/L]</td>
</tr>
<tr>
<td>312</td>
<td>0.0045</td>
<td>994</td>
<td>8.1</td>
<td>862</td>
</tr>
<tr>
<td>320</td>
<td>0.0037</td>
<td>896</td>
<td>14.0</td>
<td>857</td>
</tr>
<tr>
<td>336</td>
<td>0.0026</td>
<td>849</td>
<td>11.7</td>
<td>846</td>
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<td>781</td>
<td>9.2</td>
<td>906</td>
</tr>
<tr>
<td>415</td>
<td>0.0009</td>
<td>687</td>
<td>10.4</td>
<td>941</td>
</tr>
<tr>
<td>466</td>
<td>0.0006</td>
<td>634</td>
<td>7.3</td>
<td>929</td>
</tr>
</tbody>
</table>

**TABLE 2.2:** Fitting parameters of the models. The symbols are explained in the text.
been also done letting $n_m$, together with $b$ and $\rho_A$, vary with the temperature but no significative improvement has been observed.

The B.E.T. model gives $n_{abs}$ as a function of the fluid phase fugacity, $f$, according to:

$$n_{abs} = n_m^{abs} \cdot \frac{f/f_a}{1 - f/f_a} \cdot \frac{C}{1 + (C - 1)f/f_a}$$

(2.14)

where $n_m^{abs}$ is the monolayer capacity of the adsorbent, $C$ is a temperature dependent parameter and $f_a$ is the fugacity of the adsorbed phase, which is calculated from the adsorbed phase density and temperature (Cook, 1964). The B.E.T. model is closer to the real physical situation than the Langmuir model since the adsorbed phase is constituted of several layers. In fact, using the same number of adjusting parameters, the shape of the fitting isotherms in this case is closer to the experimental points than in the Langmuir case. How-
ever, in both cases the fitting is rather unsatisfactory despite the temperature dependence of the parameters.

Let us now analyse our data by applying a theoretical description of the density profile at the wall of the adsorbent. Blümel and Findenegg (Blümel, 1985) reported some high pressure adsorption data of SF₆ on graphite and compared them to the theory developed by Fisher and de Gennes (Fisher, 1978). They proposed an expression for the excess adsorbed amount that involves the correlation length of the bulk fluid, ξ, the critical exponents, β = 0.315 and ν = 0.63, the molecular size, a, and the monolayer coverage, nm:

\[ n^{ex} = a n_m \left[ \frac{2\nu - \beta}{\nu - \beta} \left( \frac{\xi}{a} \right)^{1 - \beta/\nu} - \frac{\beta}{\nu - \beta} \right] \] (2.15)
Using the same approach, in this work the correlation length has been calculated according to (Vesovic, 1990), the effective molecular diameter has been assumed equal to 0.3646 nm (Ben-Amotz, 1990), while $n_m$ has been expressed the product between surface area, $A$, and difference between the density of the first layer, $\rho_{ads}$, and the bulk density, i.e. $n_m = A(\rho_{ads} - \rho)$.

The fitting has been done only on the isotherms at 312 K and 320 K, since this approach can be applied up to 15 K from the critical point for the SF6/graphite system (Blümel, 1985). The two fitting parameters parameters, $A$ and $\rho_{ads}$, have been kept constant with the temperature. The value of $A$ is very similar to the one given by the manifacturer (400 m²/g) and also the value of $\rho_{ads}$ is quite reasonable. The results of the fitting are illustrated in Fig. 2.7. The agreement with the experimental points is quite good at low density, before the maximum. At high density the fitting is less satisfactory because the excess amount predicted by the model tends to zero when the bulk density approaches the adsorbed phase density of the first layer, which is kept constant for the sake of simplicity.
the whole bulk density range. Furthermore the model predicts the maximum at the critical density, while the experimental data show a maximum at a lower density. The model, in fact, has been developed for adsorption on a flat surface and the effect of geometrical confinement and irregular pore size distribution can play an important role.

Aranovich and Donohue (Aranovich, 1996) described the adsorption phenomenon using the lattice theory, by taking into account the nearest neighbours interactions in the adsorbed phase (with energy $\varepsilon_r$) and the adsorbate-adsorbent interactions (with energy $\varepsilon_A$). The corresponding isotherm can be cast as:

$$n^e = \frac{n_m}{1 - \omega_1} \left\{ \frac{x_b}{x_b + (1 - x_b) \exp(\varepsilon_A/(kT))} - x_b \right\}$$

(2.16)
where

$$\omega_1 = \alpha / 2 - \sqrt{\alpha^2 / 4 - 1}$$  \hspace{1cm} (2.17)

and

$$\alpha = - k T / [ z_2 x_b (1 - x_b) \varepsilon_f] - z_1 / z_2$$  \hspace{1cm} (2.18)

In these equations $x_b$ is the fraction of sites occupied by fluid molecules in the bulk, $n_m$ is the monolayer capacity (if the solid is not microporous), $k$ is the Boltzman’s constant, $z_0$ is the volume coordination number, $z_f$ is the monolayer coordination number and $z_2 = (z_0 - z_1) / 2$. The fitting of our experimental data has been carried out by letting $\varepsilon_f$ and $\varepsilon_i$ vary with temperature and by keeping $z_0=12$ and $z_f=6$ (hexagonal lattice). The fitting reported in Fig. 2.8 is rather good at high temperatures, but it becomes less accurate when the critical temperature is approached.

Lira and coworkers (Subramaniam, 1995), (Rangarajan, 1995) have proposed a thermodynamic model based on the so-called simplified local density (SLD) approximation, in order to describe adsorption over a large pressure range. The goal is always to find the density profile that can then be integrated using Eq (2.1). The starting point is the equality of the chemical potential of the bulk phase ($\mu_{bulk}$) and the one calculated at a point at a given distance $z$ from the wall. The latter is given by the sum of the contributions coming from the fluid-fluid interactions, $\mu_{ff}(z)$, and the one from the solid-fluid interactions, $\mu_{fs}(z)$:

$$\mu_{bulk} = \mu_{ff}(z) + \mu_{fs}(z)$$  \hspace{1cm} (2.19)

The bulk chemical potential is calculated using a proper equation of state; the solid-fluid chemical potential is given by a 10-4 Lennard-Jones potential, while $\mu_{ff}(z)$ is also given by the equation of state under the SLD approximation. Eq (2.19) is then solved to give $\rho(z)$. In the first works the van der Waals and the Peng-Robinson EOS have been used, while more recently this approach has been extended to the Elliott-Suresh-Donohue (ESD) equation of state leading to a significant improvement in quantitative accuracy.
(Soule, 2000). The results obtained are shown in Fig 2.9. In this case two temperature dependent parameters have been used in the fitting, i.e. the pore width and the solid-fluid interaction energy. Table 2.2 reports the values of the parameters used in the fitting procedure for the different models.

![Graph showing adsorption data]

**FIG. 2.9:** Fitting of the data reported in Fig 2.3 using the SLD model. The symbols are the same as in Fig 2.3.

### 2.4 Heat of Adsorption

Until now, only a few works have addressed the thermodynamic analysis of supercritical adsorption data. In most of the papers, in fact, the measured excess adsorption data are converted to absolute quantities by means of an assumption on the volume or on the density of the adsorbed phase (cf. (Agarwal, 1988)). In a few contributions, however, the excess adsorption data have been used directly to calculate heats of adsorption, according to
different definitions. These will be briefly revised and then applied to the experimental
data presented above.

First, following Specovius and Findenegg (Findenegg, 1980) let us define the enthalpy of
adsorption for an equilibrium process that occurs at constant surface potential, i.e. :

\[ \Delta H_\Phi = \frac{R}{M_w} \left( \frac{\partial \ln f}{\partial (1/T)} \right)_\Phi \]  

(2.20)

where \( f \) is the fluid phase fugacity, \( R \) is the gas constant, \( M_w \) is the molecular weight, \( T \) is
the temperature and \( \Phi \) is the surface potential that can be evaluated from the excess ad-
sorption isotherm according to the Gibbs isotherm:

\[ \Phi = -RT \int_{n_0}^{n} \ln f \, dn \]  

(2.21)

An alternative definition is adopted elsewhere and applied to data about argon, nitrogen
and methane adsorption on microporous adsorbents (Salem, 1998). The integral molar en-
thalpy change for an adsorption process that occurs at constant pressure but not at equi-
librium is given by:

\[ \Delta H_{m,int}^{\sigma} = H_{m,int}^{\sigma} - H_{m}^{\sigma} = \frac{1}{n^{ex}} \left( \frac{\partial (\Phi / T)}{\partial (1/T)} \right)_p \]  

(2.22)

where \( H_{m,int}^{\sigma} = H^{\sigma} / n^{ex} \) is the integral molar enthalpy of the adsorbed phase and \( H_{m}^{\sigma} \) is
the molar enthalpy of the gas phase; \( H^{\sigma} \) represents the excess enthalpy (adsorbed phase),
defined likewise the excess adsorbed amount of Eq (2.2).

From this quantity, the specific excess enthalpy change per mass of adsorbent can be di-
rectly calculated as:

\[ \Delta h_{sp}^{\sigma} = \frac{H^{\sigma}}{m_{ads}} = n^{ex} \Delta H_{m,int}^{\sigma} \]  

(2.23)
This definition is particularly useful, since it corresponds to the heat released during a rather simple calorimetric experiment and can thus be directly measured (Salem, 1998).

The last definition is that of the isosteric heat of adsorption, which likewise that defined for gas adsorption (Valenzuela, 1989) is the differential enthalpy for an equilibrium process that occurs at constant adsorbed amount, \( n^{ex} \) ((Salem, 1998), (Sircar, 1985b)):

\[
\Delta H^{\sigma}_{m, \text{diff}} = RZ \left( \frac{\partial \ln P}{\partial (1/T)} \right)_{n^{ex}}
\]  

(2.24)

However, the right hand side of Eq (2.24) diverges at the maximum of the excess isotherms (Salem, 1998). Since this is physically meaningless the isosteric heat of adsorption will not be considered in the following analysis.

Let us first consider \( \Delta H_{\Phi} \) defined by Eq (2.20). The Span and Wagner EOS has been used to calculate the fugacity from the measured density values at each temperature and the points \( n^{ex} \) vs. \( f \) have been fitted using as a function the ratio of fifth order polynomials. For each value of the surface potential, \( \Phi \), a plot of \( \ln f \) vs. \( 1/T \) shows that the points of all the isotherms, but those at 312 K, belong to a straight line with a correlation coefficient always larger than 0.99. Therefore data at 312 K have not been considered and \( \Delta H_{\Phi} \) has been assumed to be temperature independent.

As illustrated in Fig. 2.10, the enthalpy \( \Delta H_{\Phi} \) remains more or less constant at small values of the surface potential \( \Phi \) and decrease at larger values.

Let us now consider the integral molar enthalpy change \( \Delta H^{\sigma}_{m, \text{int}} \) defined by Eq (2.22). The derivative that appears in this equation has been estimated by fitting the experimental data \( \Phi/T \) vs. \( 1/T \) with a second order polynomial and by evaluating the derivative at each temperature. The results are plotted as a function of pressure in Fig 2.11. As it usually happens in the analysis of high pressure data, it is possible to show that the use of the density as independent variable simplifies the trends and the crossovers among the different isotherms are virtually eliminated.
It should be noted that a few irregularities in the behavior of the curves in Fig. 2.11 could be due to the computational procedure, which involves the numerical calculation of $\Phi$ through Eq (2.21) and of the derivative in Eq (2.22) using discrete data points.

In Fig. 2.12 the specific enthalpy defined by Eq (2.23) along the experimental isotherms is plotted as a function of pressure. The curves at lower temperatures exhibit a minimum that disappears when the temperature is increased. However all the isotherms seem to approach a constant value at high pressure, as already pointed out by other researchers (Salem, 1998) and the minimum value of all these curves occurs at a temperature and pressure rather close to the critical point. It is worth noting that all the curves in Fig. 2.12 are rather smooth and regular, without the unrealistic features exhibited by Fig. 2.11. It is remarkable that this occurs for the specific excess enthalpy change defined by Eq (2.23), i.e. the quantity with the clearest physical meaning.
2.5 Conclusion

In the last few years, the adsorption of supercritical fluids has attracted the interest of many researchers and many progresses have been made both in the experimental techniques and in the theoretical understanding of its peculiar features. However, many issues are still open and a considerable scientific effort is still needed to reach a deeper understanding of this phenomenon. This work has addressed the topic mainly from an experimental point of view, since only a limited number of systems have been investigated in wide temperature and pressure range (see Table 2.1). Furthermore, for some of these systems, especially when the critical temperature is approached, the accuracy of the density estimation may be low, even though it is the natural variable in the analysis of data obtained in the supercritical region. In this work, a gravimetric method with in situ density measurement has been used to obtain carbon dioxide isotherms on silica in a wide range.
of temperature (311-466 K) and pressure values (0-450 bar). The only experimental variable is the excess adsorbed amount, while the absolute adsorbed amount may be calculated with assumptions on the nature of the adsorbed phase. It has been shown that a rigorous thermodynamic treatment can be carried out on the base of the only excess amount data. Furthermore, the dynamic of an adsorption column can be described on the base of the excess adsorbed amount (Sircar, 1985a) and many models has addressed the phenomenon from this perspective, like it is shown in this work. However, the physical meaning of the different calorimetric quantities calculated in this work and presented in literature is not always clear. In particular the divergence of the isosteric heat of adsorption at the maximum of the isotherm arises some questions about the right quantity that should be used in the enthalpy balance of an adiabatic column.
2.6 Appendix

In this Appendix, the measured excess amount of carbon dioxide on silica gel is reported for the 9 supercritical and the subcritical temperature. The density is measured simultaneously as described in the text. The pressure is calculated using the Span and Wagner equation of state.
<table>
<thead>
<tr>
<th>T [K]</th>
<th>density [g/L]</th>
<th>P [bar]</th>
<th>nex [g/g]</th>
<th>T [K]</th>
<th>density [g/L]</th>
<th>P [bar]</th>
<th>nex [g/g]</th>
</tr>
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Adsorption of supercritical CO$_2$ on silica gel
In this Chapter the experimental technique illustrated in Chapter 2 have been extended to other supercritical fluids and adsorbents, thus allowing for a comparison of different fluid/adsorbent systems that enlighten the role of the physico-chemical properties of the substances in the adsorption phenomenon. A comparison with chromatographic results published in literature has also allowed the evaluation of the role of competition in the retention behavior of these systems. Furthermore, the investigation presented here has also spanned the range of near critical temperatures, leading to some peculiar features of this region, i.e. the critical adsorption and the critical depletion. It is worth to stress that both these phenomena have been already reported by other authors (cf. e.g. (Findenegg, 1997)), but it is the first time that they are investigated with an experimental set-up that allows for simultaneous density measurement, which is, in the near critical region, of fundamental importance for the reliability of the results.
3.1 Experimental technique and results

The experimental equipment and procedure has been reported in the previous Chapter. Although the measurement accuracy evaluated in section 2.2 (cf. Eq (2.9)) still applies at all the isotherms reported here and corresponding to temperature values up to 5 °C higher that the critical one, the accuracy decreases dramatically when approaching the critical point. In fact, on the one hand, the temperature could be maintained constant within an interval of 0.1 K that, in the near critical region, leads to a remarkable variation (up to 5-6%) of the fluid density. On the other hand, fluctuations of the balance signal have been observed, as a consequence of the typical near-critical density fluctuations (Levelt Sengers, 1994). Both these effects could lead, in the worse case, to an uncertainty of 20% in the excess amount adsorbed. However, this uncertainty never invalidates the observed qualitative behavior and the discussion based on it.

Three of the most commonly used supercritical fluids have been investigated: carbon dioxide (CO₂), 1,1,1,2-Tetrafluoroethane (HFC-134a) and nitrous oxide (N₂O). The properties of these fluids are summarized in Table 3.1. CO₂ and N₂O have very similar critical properties, but N₂O is slightly more polar as confirmed also by spectroscopic measurements (Loebbecke, 2000). HFC-134a has the highest critical temperature and it is more polar than the other two fluids. Three adsorbents have been used in the experiments: an unmodified silica gel (Kieselgel 60, Merck), a modified silica (Lichrospher WP 300 RP-18, Merck) and a chiral stationary phase (Chiralcel OD, Daicel). The properties of the adsorbents are reported in Table 3.2. All the possible combinations of the three fluids and the three adsorbents have been investigated, with the exception of the system HFC/Chiralcel OD because the maximum allowed temperature for the adsorbent is lower than the critical temperature of the fluid. The experimental data obtained in this work are summarized in a series of Tables reported in the Appendix 1. In Figures 3.1-Figure 3.8 the adsorption excess (in mmol/g) as a function of the fluid phase density is reported for the 7 systems fluid/adsorbent investigated in this work and for the one presented in the previous Chapter. The symbols represent the experimental points, while the continuous lines are drawn as a guide for the eyes. Because of stability problems of the adsorbent, the investigation has to be limited to 120 °C for the Lichrospher RP-18 and to 50°C for Chiralcel OD. It is worth noting that this also implies that the helium volume of these two
adsorbents has been determined at lower temperature values than for the silica gel, thus leading to a possible underestimation of it (cf. (Malbrunot, 1997) and Chapter 2).

**FIG. 3.1:** Carbon dioxide excess amount adsorbed on Kiselgel 60.
FIG. 3.2: HFC excess amount adsorbed on Kiselgel 60.

FIG. 3.3: Nitrous oxide excess amount adsorbed on Kiselgel 60.
FIG. 3.4: Carbon dioxide excess amount adsorbed on Lichrospher RP-18.

FIG. 3.5: HFC excess amount adsorbed on Lichrospher RP-18.
FIG. 3.6: Nitrous oxide excess amount adsorbed on Lichrospher RP-18.

FIG. 3.7: Carbon dioxide excess amount adsorbed on CSP.
**FIG. 3.8:** Nitrous oxide excess amount adsorbed on CSP

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**TABLE. 3.1:** Fluids properties

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**TABLE. 3.2:** Adsorbents properties
3.2 Discussion

The main focus of this work has been the characterization of the adsorption equilibria of supercritical fluids on three typical chromatographic stationary phases; this section is devoted to a detailed discussion of the main features of each system and to a comparison among them. However, it has also been noted that the three adsorbent exhibit rather different adsorption kinetics. In particular the average time needed to reach the equilibrium (defined as in the previous Chapter) was about half an hour for Kieselgel 60, a few hours for Lichrospher RP-18 and more than one day for Chiralcel OD. This behavior may be qualitatively explained on the base of the structure of the adsorbent and the relative adsorption mechanism. In fact, the adsorption sites of Kieselgel 60 are directly available on its surface, while the surface of Lichrospher RP-18 is covered by chains of 18 carbon atoms and diffusion of the fluid molecules through them is required before equilibrium can be reached. Finally Chiralcel OD exhibits the slowest kinetics because molecules must absorb and diffuse into the polymeric layer.

Let us now consider the equilibrium data. Since the chiral adsorbent Chiralcel OD is constituted by 20% by a polymer, its adsorption behavior may be affected by different phenomena compared to the two silica-based materials. For this reason we will carried out the discussion of the results concerning Kieselgel 60 and Lichrospher RP-18 separately from the Chiralcel OD.

3.2.1 Kieselgel 60 and Lichrospher RP-18

All the isotherm show a maximum and, at high density values, they tend to approach a constant asymptotic value. A thorough discussion of the capability of the models present in literature to describe this shape and to give a quantitative prediction has been reported in the previous chapter.

Critical adsorption and critical depletion

Let us now focus on the main features that arise, when the temperature \(T\) approaches the critical one \(T_c\). For all the systems investigated the amount adsorbed increases strongly in the region close to the maximum when \(T \to T_c\) (‘critical adsorption’). The second phe-
nomenon is the so-called ‘critical depletion’, which consists in a decrease of the amount adsorbed in the region close to the critical density, and its appearance depends on the particular system investigated. Both these phenomena have been already reported in literature for systems different from ours and have been theoretically investigated. However, as pointed out at the beginning of this Chapter, this is the first time that they have been investigated with a simultaneous measurement of adsorbed amount and density. In fact, it is well known that close to the critical temperature large deviations from the actual density value may arise when it is estimated from temperature and pressure measurements using an equation of state. Therefore these results eliminate any remaining doubt about the real occurrence of these two phenomena and confirm the qualitative features of the previous findings. In the following the main works dealing with these two phenomena are reviewed and the experimental results are analyzed in this perspective.

In 1978 Fisher and De Gennes (Fisher, 1978) showed that, on an attractive wall in contact with a semiinfinite plane, the amount adsorbed diverges when the bulk critical point is approached. A pronounced increase of the surface excess amount on approaching the critical point has been then observed while measuring the adsorption of ethylene on graphitized carbon (Specovius, 1980). Another experimental confirmation has come from the measurement of the surface excess amount of SF$_6$ on graphitized carbon black along an isochoric path (Blümel, 1985). The exponential divergence of the amount adsorbed predicted by the Fisher-de Gennes scaling theory has been verified, but with a higher exponent compared with the theoretical one.

The occurrence of this phenomenon can be clearly seen also in our results, especially for the systems where the lowest temperatures have been investigated. Let us focus, for example, on the adsorption of CO$_2$ on Lichrospher RP-18. A decrease of 15°C close to the critical temperature (from 320 K to 305 K) causes an increase of the adsorption maximum of 135%, while the same decrease of 15°C from 335 K to 320 K causes an increase of only 30%.

The so-called critical depletion, instead, has been found for the first time experimentally (Thommes, 1994b) and then several theoretical works have attempted to give a reasonable explanation to this apparently unusual phenomenon. The first systems to be investigated have been SF$_6$ on finely divided graphite substrate (Thommes, 1994b) and on controlled-pore glass (Thommes, 1994b) (Thommes, 1995). A rather intuitive explanation (the so-
called "Gedankenexperiment") is based on the fact that the geometrical confinement of the pores causes a shift to a lower value of the critical temperature of the so-called ‘pore phase’ compared to the ‘bulk phase’. Therefore, in order to maintain the mechanical stability between the two phases, the pressure must be the same and, as a direct consequence, the density of the ‘pore phase’ must be lower (Schoen, 1995),(Schoen, 1997). Appendix 3 of this Chapter is dedicated to a review of the "Gedankenexperiment". As it has been shown in Monte Carlo simulations, the density in the center of the pores (the so-called ‘core’ region) exhibits a depletion compared to the bulk density, while, close to the wall (‘wall region’) the density is higher, because of the attractive force of the surface potential (Schoen, 1995),(Schoen, 1997). If this description of the phenomenon is accepted, it is clear that the occurrence of critical depletion depends basically on two elements. On the one hand the pore geometry of the adsorbent determines both the extension of the ‘core’ region where density depletion may occur and the shift of the critical temperature that is inversely proportional to the pore diameter, $D$, according to (Fisher, 1981):

$$\Delta T_c = \frac{A}{D^\gamma} \quad (3.1)$$

where $A$ is a system dependent empirical coefficient, while $\gamma$ should be an universal constant equal to 1.6. Experimental investigation of SF$_6$ on controlled-pore glass have confirmed the qualitative prediction of Eq (3.1), but the exponent $\gamma$ has been found to be higher than 2 (Thommes, 1994a).

On the other hand, the strength of the solid-fluid potential determines the magnitude of the increase of density close to the wall. Recently, it has been shown that the results of these Monte Carlo simulations may be not accurate because of systematic errors associated with the use of long range corrections for the potential truncation (Wilding, 1999). Another group of researchers has shown that this phenomenon may arise from the competing effects of bulk and surface fields (Macioleck, 1998). However, a deeper analysis has lead to opposite conclusions, i.e. a single pore model is never able to account for critical depletion (Macioleck, 1999), which is more likely to arise from the complex morphology of interconnected pores of different sizes and shapes that constitute the adsorbent materials. A recent work (Kiselev, 2000) has attempted to model this phenomenon using a crossover theory, but a satisfactory fitting of the experimental data could not be achieved for tem-
temperatures very close to the critical one. Furthermore the values of the parameters that realize the best fitting correspond to the so-called “ordinary” transitions, while the theory predicts, for a fluid against a hard wall, a surface critical behavior in the universality class of “normal” transition. From this brief review, it is clear that no satisfactory explanation has been found yet, since the complex geometry of the real system is never taken into account in all these simplified models. However, even if the phenomena that play a role may be more complex and other elements may be considered, the explanation given in (Schoen, 1995), (Schoen, 1997) remains the only one where a clear, even if simplified, physical picture allows a qualitative discussion on experimental results to be carried out.

Let us now consider our measurements. Critical depletion is observed with all the three fluids with Lichrospher RP-18, while only N\textsubscript{2}O exhibits depletion on Kieselgel 60. It is worth noting that, when considering the system CO\textsubscript{2}/Kieselgel 60, the range of temperatures investigated may have been too far from the region where a shift of the critical point can be observed in the pore phase; in fact the minimum experimental temperature investigated has been of 311.9 K, i.e. 7.8 K higher than the critical temperature. However, the same explanation is not satisfactory when considering the adsorption of HFC, since at the same temperature of 377.5 K it exhibits depletion when adsorbed on Lichrospher RP-18. The pore diameter of this adsorbent is five times larger than Kieselgel 60 and this has two main consequences. On the one hand, the shift of the critical temperature should be less evident (cf. Eq. (3.1)) but, on the other hand, more space is available for the extension of a ‘core’ region compared to a ‘wall’ region. Furthermore, the attractive potential of the wall of Kieselgel 60 is stronger (see below) than the modified silica, so that the increase of density due to the wall attraction may be dominant compared to the depletion.

It is worth noting that the two phenomena, i.e. critical adsorption and depletion, may act at the same time and may produce a non monotonic variation of the amount adsorbed as a function of the temperature at constant density (isochoric path). Let us consider again the adsorption of CO\textsubscript{2} on Lichrospher RP-18 and let us focus on density values around the CO\textsubscript{2} critical density (467 g/L). Along an isochoric path, when the temperature is decreased, the excess adsorbed amount first increases, then decreases (cf. isotherm at 309 K) and then increases again. It seems reasonable that the effect of the critical depletion is maximum for temperature values close to 309 K and then the critical adsorption prevails, leading to an increase of excess adsorbed amount at temperatures closer to the critical one.
Comparison between adsorbents (same fluid)

Let us consider the adsorption of the same fluid on the two different adsorbents. Let us focus, in particular, on the adsorption of carbon dioxide, but similar considerations apply to the other fluids. In order to compare the two systems, the difference in surface area must be taken into account and the amount adsorbed on Lichrospher RP-18 must be multiplied by a factor 5. The adsorption on modified silica is, even after this correction, in general higher than the one on Lichrospher RP-18.

![Graph](image_url)

**FIG. 3.9:** Adsorbed amount of the isotherms maxima for CO$_2$ on Kieselgel 60 and Lichrospher RP-18 as a function of temperature.

However, the difference is larger at higher temperatures and decreases when approaching the critical point as we can see in Fig 3.9, where the difference between the maxima of the isotherms on the two adsorbents is reported as a function of temperature. These results may be a further confirmation of the occurrence of a ‘critical adsorption’ phenomenon.
that has an universal character, independent of the specific fluid-wall potential of the system.

Comparison between fluids (same adsorbent)

Let us now consider the adsorption of two fluids (CO$_2$ and N$_2$O) on the same adsorbent (Kieselgel 60). In Fig 3.10, the isotherms at 312, 350 and 466 K for the two fluids are reported on the same graph for comparison.

The isotherms of the two fluids are very similar, when high temperature values are considered. However, when the critical point is approached, the behavior of the two fluids at the same temperature is rather different. At 312 K, N$_2$O is already close to its critical temperature, while, for CO$_2$, the critical region is still far. Therefore, the isotherm of N$_2$O exhibits a more pronounced maximum because of the ‘critical adsorption’, while, for values around the critical densities, the adsorption of CO$_2$ is larger, since ‘critical depletion’ oc-
curs in the N₂O/Kiselgel system. When the adsorption of CO₂ and N₂O on Lichrospher RP-18 is considered (cf. Fig 3.11), similar considerations apply, namely the difference between the isotherms of the two fluids increases when the critical point is approached. However, on the one hand, the adsorption isotherm of N₂O is always higher than the one of CO₂ at the same temperature and, on the other hand, the increase of adsorption for the N₂O/Lichrospher RP-18 system is already remarkable at a temperature more than 10 K higher than the critical one.

![Graph showing adsorption comparison](image)

**FIG. 3.11**: Comparison between CO₂ and N₂O on Lichrospher RP-C18 at two different temperature values

A comparison between the adsorption of CO₂ or N₂O and HFC is less straightforward, since the molecular weight of HFC is more than the double of the one of the other two components. For this reason, the measurements are expressed in mmol/g, even if also this choice may be questionable. In fact, in this way, one may expect that less moles of HFC can be accommodated on the same surface, since the HFC molecule is much larger than CO₂ or N₂O. However, the adsorption of HFC is always larger than the one of the other two components at the same temperature. This implies that the surface potential for HFC is higher and the adsorbed phase is constituted of more layers than for the other two fluids.
It is worth noting that, also in this case, the difference in the amount adsorbed, compared to the other two fluids, is higher when the critical temperature of HFC is approached.

3.2.2 Chiralcel OD

Chiralcel OD is constituted by a phenylcarbamate derivative of cellulose coated on macroporous silica gel. The polymer represents about 20% of the total weight of the adsorbent and it is distributed on the whole silica surface as a layer of about 12 nm. Therefore, the fluid molecules interact with the three-dimensional structure of the polymer, in contrast to the other two adsorbents where the molecules interact basically with the surface. This phenomenon is usually indicated as “absorption” or “sorption”. It is worth noting that the absorption of supercritical fluids on polymeric materials has attracted the attention of many researchers for its importance in polymer processing (Royer, 1999) and controlled drug release (Kikic, 1999). Supercritical fluids, in fact, may significantly modify the polymer properties when they absorb and swell them. The adsorbed amount of carbon dioxide on PET (poly-ethylene-terephthalate) has been measured simultaneously to the swelling of the polymeric sample using a Rubotherm magnetic suspension balance with a view cell [von Schnitzler, 1999 #447]. However, it is worth noting that information about the polymer swelling is not necessary to obtain excess adsorbed amount data. In fact the increase of the polymer volume is equivalent to the volume of the adsorbed phase, $V_a$, which is unknown also in the case of adsorption on non-swellable materials. Thus, summarizing, although a different interaction mechanism is expected, the measurements on Chiralcel OD have been obtained with the same procedure and have the same physical meaning as the ones on Kieselgel 60 and Lichrospher RP-18.

The investigation with N$_2$O was limited to two temperature values (cf. Fig 3.8) since the maximum temperature for the adsorbent was only a few degrees higher than the critical temperature of the fluid. The shape of the isotherms is similar to the one obtained for other systems (cf. for example HFC/Lichrospher RP-18), but it is the first time that critical depletion has been observed in macroporous materials. In this case, in fact, the shift of the critical temperature inside the pores should be minimum (cf. Eq (3.1)) and so also the shift of the density in the “core” region inside the pores compared to the bulk density. On the base of the only measurements presented in this work, it is not clear if a phenomenon different from the previous observed “critical depletion” occurs because of the polymeric
layer. An answer to this question may come from measurements on a non-coated macro-
porous silica.

Excess adsorption isotherms of CO$_2$ on Chiralcel OD (Fig 3.7) exhibits a behavior similar
to CO$_2$/Lichrospher RP-18 (cf. ) in which depletion appears at intermediate temperature
values. In the previous section, a qualitative interpretation based on the competition be-
tween critical adsorption and depletion has been presented, but this unusual phenomenon
deserves a deeper experimental and theoretical investigation.

### 3.3 Comparison with chromatographic data

The knowledge of adsorption data of a single component is of interest also for the analysis
of the adsorption behavior of fluid mixtures, which is basically determined by two ele-
ments: on the one hand, the nonidealities in the fluid and adsorbed phase and, on the other
hand, the competition of all the components. A thorough study of this phenomenon is still
lacking and it is the objective of the future work of our research group. This requires the
measurement of the single component isotherms of all the components that constitute the
mixture, the characterization of the fluid phase behavior (in order to determine the fugac-
ity of each component in the fluid phase) and the interpretation with a sound thermody-
namic model (like the RAST model (Larionov, 1971)) in which only excess properties for
the adsorbed phase are required. However, from the measurements of different supercrit-
cical solvents on the same adsorbent presented in this work and from published works
about the chromatographic behavior and the solubility data of some mixtures, some qual-
itative considerations on the adsorption of those mixtures may be drawn.

Chromatographic measurements represent a rapid and simple method to obtain informa-
tion about the relative adsorption of the different components that constitute a mixture.
Moreover, when considering the retention of the same solute eluted by two different sol-
vents, at least qualitative information about the adsorption isotherm of this component un-
der these two different conditions may be obtained. To our knowledge, only few works
have addressed the issue of comparing the elution of the same solute with different super-
critical fluids. As it is illustrated in Fig 3.12, the retention time of chrysene on unmodified
silica is always larger when the solvent is sc-CO$_2$ than when it is sc-N$_2$O and this differ-
ence reaches a maximum at about 120 °C (Leyendecker, 1987). There may be in principle
two main reasons for this behavior: the adsorption of N\textsubscript{2}O is larger than CO\textsubscript{2} leading to a larger competition with the solute in the adsorption on the silica or the affinity towards the fluid phase of chrysene when N\textsubscript{2}O is used, i.e. its solubility, is higher than in CO\textsubscript{2}. Let us now consider the measurements of the adsorption excess amounts of CO\textsubscript{2} and N\textsubscript{2}O on Kiselgel 60 that are compared in Fig 3.10. The isotherms of the two sc-fluids are almost coincident at high temperatures and a significant difference appears only close to the N\textsubscript{2}O critical point. If we neglect nonidealities in the adsorbed phase, e.g. we assume an Ideal Adsorption Solution (IAS) model (Myers, 1965), the solvent competition does not seem to be responsible for the stronger adsorption of chrysene when it is eluted in sc-CO\textsubscript{2} with respect to sc-N\textsubscript{2}O. In fact, according to Fig 3.12 the difference in the adsorption behavior is larger at high temperature, where the single component isotherm are coincident. However, N\textsubscript{2}O has been shown to be a better solvent than CO\textsubscript{2} for nonpolar molecules like β-
carotene (cf. (Subra, 1997)). In the absence of any specific molecular interactions like hydrogen bonding, the dipole moment may become dominant in determining solvent properties. These considerations apply also to chrysene that is a large nonpolar molecule (cf. Fig 3.12). We can therefore conclude that the behavior observed in (Leyendecker, 1987) is essentially determined by an higher solubility in the fluid phase rather than a competition effect.

Although most of the data required for a rigorous thermodynamic treatment of the adsorption of a supercritical mixture are still missing and no quantitative description can be carried out, it has been shown how single component adsorption data and solubility measurements may be used to rationalize the chromatographic behavior of a solute eluted with different supercritical fluids. On the base of these considerations, we should expect that, when the three sc-fluids investigated in this work are compared, HFC is the one for which the retention time of a solute would be the smallest since its adsorption (cf. above) and its solvent power (cf. (Abbot, 1999)) are the largest. In fact, it has been shown that the elution of several naphtalene derivatives on a bare silica column is much faster when HFC-134a is used rather than CO₂, even when a modifier is added (Cantrell, 1997).

### 3.4 Concluding remarks and future work

In this work the measurements of different adsorption systems has allowed both the comparison among materials and fluids with different properties and the investigation of the peculiar features of the near critical region. Furthermore, it has been shown that a phenomenological interpretation of the qualitative behaviors and trends can be obtained using theories present in literature. However, we believe that these aspects deserve a deeper experimental and theoretical analysis in the future.

Section 3.3 of this Chapter has addressed the important issue of the adsorption behavior of mixtures. In particular, the comparison between single component adsorption data obtained in this work with solubility and chromatographic data published in literature has allowed the qualitative behavior of mixtures to be discussed. In order to predict in a quantitative way the adsorption of mixtures further experimental work is needed.
In fact, the next step needed for the application of a sound thermodynamic approach to these systems is to obtain reliable data of fluid mixtures where the competitive adsorption isotherms of all the solutes and of the solvent can be measured. We believe that the adsorption-desorption method (Talu, 1986) may be well adapted to the measurement of adsorption equilibria under supercritical conditions. The Real Adsorption Solution Theory (RAST) may be then applied to correlate the data available (single component isotherms, competitive isotherms and information about the fluid phase behavior) and give predictions on the behavior of these systems. It is worth noting that the equations of the RAST may be recast in term of excess amount adsorbed without any assumption on the nature of the adsorbed phase (the equations are reported in the Appendix 2 of this Chapter).

**Appendix 1**

In this Appendix, the measured excess amount is reported for the 7 systems investigated in this work. The density is measured simultaneously as described in the Chapter 2. The pressure values have been calculated using the Span and Wagner equation of state (Span, 1996) for CO$_2$ and (Tillner-Roth, 1994) for HFC-134a.
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**TABLE 3.6:** *HFC on Lichrospher RP-18*
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**TABLE 3.8:** CO$_2$ on Chiralcel OD
Appendix 2

The goal of this Appendix is to show that the equations of the RAST theory (Talu, 1988) may be recast in terms of excess properties and therefore directly applied to the experimental data. It is worth noting that these equations have been derived in the theoretical framework proposed by (Sircar, 1985a). Therefore, for the sake of clarity, the symbols used in this Appendix are consistent with the ones used in (Sircar, 1985a) but they are different from the ones used in the other parts of this dissertation.

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**TABLE 3.9: \( N_2O \) on Chiralcel\textit{OD}**
Introduction and definitions

The Gibbs-Duhem equation for the adsorbed phase (absolute quantities with a prime):

\[ 0 = s'dT - v'dP + \sum_{j} x'_j d\mu'_j + \frac{d\Phi}{n'} \]  

(A.1)

Multiplying by \( n' \) yields:

\[ 0 = S'dT - V'dP + \sum_{j} n'_j d\mu'_j + d\Phi \]  

(A.2)

Following the notation used by Ruthven (1984), in which \( n_a \) moles of adsorbent are considered, in the system, \( (-n_a d\phi) \) is used instead of \( d\Phi \).

\[ 0 = S'dT - V'dP + \sum_{j} n'_j d\mu'_j - n_a d\phi \]  

(A.3)

Accordingly the Gibbs-Duhem equation for the adsorbed phase using excess variables (superscript \( m \)) can be cast as:

\[ 0 = s^m dT + \sum_{j} n^m_j d\mu_j - n_a d\phi \]  

(A.4)

and the Gibbs free energy:
\[ g^m = -\phi n_a + \sum_i n_i^m \mu_i \]  
(A.5)

\[ dg^m = -s^m dT + \sum_i \mu_i dn_i^m - \phi dn_a \]  
(A.6)

Following Hill (cited by Ruthven), it is useful to define a new thermodynamic function:

\[ G_H^* = G^* + \phi n_a \]  
(A.7)

that in term of excess properties can be written as:

\[ g_{H_H}^m = g^m + \phi n_a = \sum_i n_i^m \mu_i \]  
(A.8)

Using Eq (A.4) yields:

\[ dg_{H_H}^m = -s^m dT + \sum_i \mu_i dn_i^m + n_a d\phi \]  
(A.9)

The following relationship involving a newly defined ‘partial molar quantity’, \( \bar{n}_{ai} \), is obtained:
From Eq (A.4) at constant T and for a single component, one obtains:

\[
\begin{align*}
\left( \frac{\partial \mu_i}{\partial \phi} \right)_{T, n_i^m} &= \left( \frac{\partial}{\partial \phi} \left( \frac{\partial g_H^m}{\partial n_i^m} \right) \right)_{T, \phi, n_j^m} T, n_i^m \\
&= \left( \frac{\partial}{\partial n_i^m} \left( \frac{\partial g_H^m}{\partial \phi} \right) \right)_{T, \phi, n_j^m} T, n_i^m \\
&= \left( \frac{\partial n_a}{\partial n_i^m} \right)_{T, \phi, n_j^m} = n_{ai}
\end{align*}
\]

(A.10)

**Fugacity**

From Eq (A.4) at constant T and for a single component, one obtains:

\[
d\mu = \frac{n_a}{n_i^m} d\phi
\]

(A.11)

Let us define the excess surface concentration

\[
\Gamma^m = \frac{n_i^m}{n_a}
\]

(A.12)
If the molecules in the adsorbed phase are assumed to exhibit ideal behaviour (cf. Ideal Gas law), the corresponding equation of state can be written as:

$$\phi = \Gamma^{-1}RT$$ (A.13)

Combining the last 3 equations yields:

$$d\mu = RTd\ln\phi$$ (A.14)

If the adsorbed phase is not ideal the chemical potential can always be written as a function of the fugacity.

$$d\mu = RTd\ln f$$ (A.15)

For an ideal mixture, the fugacity of component $i$ can be expressed by the linear relationship:

$$\tilde{f}_i = f_i^0 x_i$$ (A.16)

where $f_i^0$ is the fluid phase fugacity of the pure component at the $T$ and $\phi$ of the mixture. It follows that:

$$\left(\frac{\partial}{\partial \phi} \ln \tilde{f}_i\right)_{T, \eta_i} = \left(\frac{\partial}{\partial \phi} \ln f_i^0\right)_T$$
and therefore:

\[ n_{ai} = n_{ai}^0 \]  \hspace{1cm} (A.17)

It is worth noting that from Eq (A.12) one defines the excess concentration for a pure component as:

\[ \Gamma_{i, m^0} = \frac{n_{i}^{m^0}}{n_{a}} \]  \hspace{1cm} (A.18)

**IAST with excess properties**

Since

\[ n_a = \sum_i n_{ai} n_i^{m^0} \]

and using Eqs (A.12), (A.17) and (A.18) we obtain:

\[ \frac{1}{\Gamma_{m}^{m^0}} = \sum_i \frac{x_{i}^{m}}{\Gamma_{i, m^0}} \]  \hspace{1cm} (A.19)

Therefore the equations giving adsorbed phase properties in terms of fluid phase fugacities are:
Adsorption of supercritical fluids on mesoporous adsorbents

\[ f_i^G = f_i^0 x_i^n \]

\[ \phi = RT \int_0^{m_i} \Gamma_i \ln f_i \, d\Gamma_i \]

\[ \sum_i x_i^n = 1 \]

\[ \frac{1}{\Gamma_i^n} = \sum_i \frac{x_i^n}{\Gamma_i^0} \]

\[ \Gamma_i^n = \Gamma_i^m x_i^n \]

**Nonideal adsorbed phase**

Introducing the activity coefficients to take nonideality into account, the chemical potential is:

\[ d\mu_i = d\mu_i^0 + RT \ln \gamma_i \]  \hspace{1cm} (A.20)

Dividing Eq (A.4) by \( n^m \) at constant T yields:

\[ \frac{d\phi}{\Gamma_i^n} = \sum_i x_i^n d\mu_i \]  \hspace{1cm} (A.21)
The same equation for an ideal mixture at the same temperature and surface potential is:

\[
\frac{d\phi}{\Gamma_{id}^m} = \sum_j x_j^m d\mu_{i,jid}
\]  

(A.22)

where \(\Gamma_{id}^m\) is the excess concentration for an ideal mixture that can be calculated according to Eq (A.19).

Combining the last two equations we obtain:

\[
\frac{1}{\Gamma^m} - \frac{1}{\Gamma_{id}^m} = RT \sum_j x_j^m \frac{\partial}{\partial \phi} \ln \gamma_i
\]

**RAST with excess properties**

The system to be solved will be:

\[
f_i^G = f_i^0 x_i^m \gamma_i
\]

\[
\phi = RT \int_0^{\Gamma_i^0} d\ln f_i
\]

\[
\sum_i x_i^m = 1
\]

\[
\ln \gamma_i = \ln \gamma_i^* (1 - e^{\alpha_0})
\]
The activity coefficients $\gamma_i^m$ can be calculated using one of the empirical models developed for liquid phases (e.g. van Laar, Margules), where the excess molar fractions are plugged in.

\[
\frac{1}{\Gamma_i^m} = \sum_i \frac{x_i^m}{\Gamma_i^0} + RT \sum_i \frac{x_i^m}{\partial \Phi} \ln \gamma_i
\]

\[
\Gamma_i^m = \Gamma_i^w x_i^m
\]

The activity coefficients $\gamma_i^m$ can be calculated using one of the empirical models developed for liquid phases (e.g. van Laar, Margules), where the excess molar fractions are plugged in.

**Appendix 3**

Goal of this Appendix is to review the so-called "Gedankenexperiment" (Schoen, 1995) which gives a rather simple and convincing explanation of the phenomenon of critical depletion.

Let us consider a composite system constituted of an infinitely large bulk reservoir in thermodynamic and mechanical equilibrium with a fluid confined between two parallel walls at a distance $s$. Let us assume that the distance $s$ between the walls is large enough (mesoporous adsorbents) to allow for the development of a "wall region", where the wall attractive potential leads to a fluid density profile, and a "core region" in the center of the pore, where the wall potential has no effect. Thus summarizing, the system is constituted of three phases in equilibrium: the bulk, the "core region" and the adsorbed phase ("wall region"). The surface excess is determined by the density in the bulk and the average density in the pore. Usually the core region does not differ from the bulk region and the density in the pore is higher than the density in the bulk, if the wall exhibits an attractive potential. Therefore, at constant bulk density, the surface excess increases when temperature decreases, since the wall potential becomes stronger and the adsorption is an exothermic process. However, it is possible to show that, close to the critical point, the core region differs from the bulk region. In particular the core region exhibits a lower density.
and the net effect is a decrease of the surface excess when temperature decreases, although the density of the adsorbed phase is larger than the one in the bulk.

Let us now show that, when the critical point is approached, the density in the core region becomes lower than the one in the bulk. Let the bulk and pore phases experience the following situations:

1) The two systems are initially at high temperature $T$ and in contact one with each other. Therefore both the density and the correlation length are the same:

$$ \rho_{\text{core}} = \rho_{\text{bulk}} $$

and

$$ \xi_{\text{core}} = \xi_{\text{bulk}} < s $$

2) The temperature is lowered to a value $T = T_0$ so that the correlation length increases and reaches the same order of magnitude of $s$ and, inside the pore, it cannot increase anymore.

3) The bulk and the pore systems are then separated and the temperature is further decreased to $T' = T_0 - dT$. While the correlation length in the bulk can increase indefinitely, $\xi_{\text{core}}$ is upper bounded by the pore dimension $s$ and therefore at this temperature:

$$ \xi_{\text{core}} < \xi_{\text{bulk}} $$

Let us consider the fluctuations theorem that relates the fluid microscopic properties to the compressibility $K_T$ (Levelt Sengers, 1991):

$$ \tilde{\rho} k T K_T = 1 + \tilde{\rho} \int_V (g(r) - 1) dr $$  \hspace{1cm} (A.23)

where $\tilde{\rho}$ is the number density (number of molecules per unit volume), $k$ is the Boltzmann constant and $g(r)$ is the correlation function which for large $r$ decays according to:

$$ g(r) = \frac{\exp \left( -\frac{r}{\xi} \right)}{r}. $$
When comparing the correlation function in the bulk and in the pore, the two functions are the same for small \( r \) (the short range behavior is determined only by the intermolecular potential that is the same at the same \( T \)) and differ only in the "tail". Since the decay parameter \( \xi \) is larger in the bulk, the integral on the r.h.s. of Eq (23) is larger and therefore:

\[ K_{T, \text{core}} < K_{T, \text{bulk}} \]

Let us now show that the last inequality implies:

\[ P_{\text{core}} > P_{\text{bulk}} \]

In fact the van der Waals equation of state:

\[ P = \frac{\rho}{1 - \rho b} kT - \rho \alpha \rho^2 \]

can be recast as follows:

\[ \frac{P}{kT} = \rho \left[ \frac{1}{1 - \frac{3}{4} l} - \frac{9}{8} l t \right] \]

where \( l = l_{\text{bulk}} = \rho/\rho_{c, \text{bulk}} \) or \( l = l_{\text{core}} = \rho/\rho_{c, \text{core}} \) and \( t = T_{c, \text{bulk}}/T \) or \( t = T_{c, \text{core}}/T \), respectively. Similarly from Eq (A.24) one obtains:

\[ \frac{K_T^{-1}}{kT} = \rho \left[ \frac{1}{\left(1 - \frac{3}{4} l \right)^2} - \frac{9}{4} \frac{l}{4} \right] \]

where \( K_T = -1/V (\partial V / \partial P)_T \). Since we have made the transformation \( T_0 \to T' \) along the critical isochore of the bulk fluid \( (l_{\text{bulk}} = 1) \) and because \( dT' \) is infinitesimally small, we can recast Eqs. (A.24) and (A.25), expanding the first therm in brackets in a Taylor series around \( l_{\text{core}} = 1 \). Eq (A.25) yields:

\[ \frac{K_{T, \text{core}}^{-1} - K_{T, \text{bulk}}^{-1}}{kT} = \frac{9}{4} \rho_{c, \text{bulk}} (l_{\text{bulk}} - l_{\text{core}} l_{\text{core}} - (1 - l_{\text{core}})) > 0 \]
while from Eq (A.24) one obtains:

\[
\frac{P_{\text{core}} - P_{\text{bulk}}}{kT} = \frac{9}{8} \rho_{c,\text{bulk}} \left[ t_{\text{bulk}} - t_{\text{core}} t_{\text{core}} - \frac{2}{3} (1 - t_{\text{core}}) \right] > 0
\]  

(A.27)

which must be positive since the r.h.s. of Eq (A.26) is a positive quantity.

4) Let us now reconnect the two systems. In order to reestablish the mechanical stability, matter must flow from the core to the bulk until \( P_{\text{core}}(\rho_{\text{core}}, T) = P_{\text{bulk}}(\rho_{\text{bulk}}, T) \), leading to a decrease of the density in the core region.

Thus summarizing, although the attractive potential of the wall leads to a local increase of the density in the "wall region", the geometry confinement leads to a depletion in the "core region" when the critical temperature is approached and the net effect is the decrease of the surface excess that is experimentally observed.
Triangle theory is nowadays a well established method to predict the behavior of SMBs and optimize their performance. However this theory has been developed for SMBs operating with liquid solvents, i.e. with an incompressible fluid phase. It is worth noting that, if pressure drop may be considered negligible, the density along a SF-SMB unit operating in isocratic mode (cf. section 1.3) is constant and the behavior is the same as in the liquid case. The aim of this chapter is to extend the so-called triangle theory to a SF-SMB unit operating in pressure gradient mode and with negligible pressure drop along the columns. In this case, the compressibility of the fluid phase plays an important role not only on the volumetric flowrates, but also on the adsorption equilibria. Recently, criteria for the design of optimal and robust operating conditions for an SF-SMB unit, where linear adsorption equilibria apply, have been presented (Mazzotti, 1997a). However, SMBs are most beneficial when operated under overload conditions, since when increasing the overall feed concentration of the compounds to be separated, both productivity and solvent con-
sumption of the process improve. However, this usually implies to operate the unit in the region of nonlinear competitive adsorption equilibria. Accordingly, in this chapter we investigate the opportunities offered by the SF-SMB technology by deriving criteria for the design of binary separations under nonlinear overload conditions and using them to optimize the separation performance.

In order to extend the triangle theory to the design of an SF-SMB separation carried out in the pressure gradient mode, two main features have to been taken into account. On the one hand, the adsorption thermodynamics depends on the density level in each section of the unit and therefore different isotherms have to be used in the different sections of the unit. On the other hand, rather complex fluiddynamic phenomena occur at the beginning of each time period when the valves and the columns switch and the set-point pressure values in each SMB section have to be reached and stabilised.

In section 4.1 a short background on the triangle theory is given. Then, the models used to describe the adsorption equilibria corresponding to different density levels are presented and discussed in section 4.2. The design criteria for SF-SMB units will be derived in section 4.4 using the same approach adopted for an SMB unit where different temperature values are imposed in the different sections (Migliorini, 2000b). However, in order to apply this approach, the criteria that guarantee the equivalence between an SF-SMB and a SF-TMB unit need to be thoroughly discussed; section 4.3 is devoted to this key issue. Finally, in section 4.5, an analysis of the SF-SMB performance is carried out in order to determine optimal operating conditions.

### 4.1 Background on the triangle theory

In this section the basic ideas of the triangle theory are illustrated with reference to the classical case where a non-compressible fluid phase is used. The key idea in the Simulated Moving Bed (SMB) technology is to simulate the countercurrent motion of the solid phase with respect to the fluid phase by periodically switching the inlet and outlet ports of the unit in the same direction of the fluid flow (see Section 1.1). The SMB unit (Fig 1.2) and the true counter-current unit (TMB, Fig 1.1) achieve the same separation performance if the following equivalence conditions are fulfilled:
\[ Q_j^{\text{TMB}} = Q_j^{\text{SMB}} + Q_s \cdot \frac{\varepsilon_b}{1 - \varepsilon_b} \]
\[ Q_s = (1 - \varepsilon_b) \cdot \frac{V}{t^*} \]  

(4.1)

In these equations, \( Q_j^{\text{TMB}} \) is the fluid volumetric flow rate in section \( j \) of the TMB unit, \( Q_j^{\text{SMB}} \) is the fluid volumetric flow rate in section \( j \) of the SMB unit, \( Q_s \) is the solid volumetric flow rate in the TMB unit, \( V \) is the column volume and \( \varepsilon_b \) is the external porosity of the packed bed. \( t^* \) is the port switching period and in the following it is referred to as the switch time. These equivalence relationships hold in cyclic steady state conditions and can be used to study the performance of an SMB unit by considering the steady state of the equivalent TMB unit.

By applying equilibrium theory, i.e. by neglecting axial dispersion and mass transfer resistance, it is possible to calculate simple conditions leading to different separation regimes (cf. (Storti, 1993), (Mazzotti, 1994), (Mazzotti, 1996a), (Mazzotti, 1997b), (Mazzotti, 1997c), (Chiang, 1998a), (Chiang, 1998b), (Migliorini, 2000a)). These simple relationships are expressed in terms of the dimensionless parameters \( m_j \), defined as the ratio between the net fluid and solid flow rates in each section of the unit:

\[ m_j = \frac{Q_j^{\text{TMB}} - \varepsilon_p Q_s}{Q_s (1 - \varepsilon_p)} \]  

(4.2)

where \( \varepsilon_p \) is the internal porosity of the column packing material. These conditions can be represented graphically by drawing boundaries in the \((m_2, m_3)\) plane, which identify several regions corresponding to various separation regimes: both, raffinate and extract are pure (complete separation); only one pure outlet, either extract or raffinate; no pure outlet (see Fig 4.1). Due to the shape of the complete separation region this approach is often indicated as the “Triangle Theory” and it has been validated by comparison with experimental data (cf. (Pedeferri, 1999), (Storti, 1993), (Mazzotti, 1996b)) and applied to investigate various separations (cf. (Mazzotti, 1997c), (Francotte, 1998)).

Let us briefly summarize the procedure adopted to derive these criteria. In the frame of equilibrium theory the mass balance equation for the \( i \)-th species in the \( j \)-th section of the TMB unit can be written as follows:
\[ \frac{\partial}{\partial t} [\varepsilon c_{i,j} + (1 - \varepsilon)n_{i,j}] + \frac{\partial}{\partial z} [uc_{i,j} - u_s(e_p c_{i,j} + (1 - e_p)n_{i,j})] = 0 \] (4.3)

where \( u \) is the fluid superficial velocity, \( u_s \) is the solid superficial velocity (\( Q_s \) divided by the column cross section), \( \varepsilon = \varepsilon_b + (1 - \varepsilon_b)e_f \) is the total porosity of the column, \( c_{i,j} \) is the fluid concentration of the \( i \)-th component in the \( j \)-th section, \( n_{i,j} \) is the concentration of the \( i \)-th component on the solid in the \( j \)-th section, \( t \) is time and \( z \) is the axial coordinate.

This equation can be rearranged in a convenient way as:

\[ \frac{\partial}{\partial t} [\varepsilon c_{i,j} + (1 - \varepsilon)n_{i,j}] + u_s(1 - e_p)\frac{\partial}{\partial z} [m_j c_{i,j} - n_{i,j}] = 0 \] (4.4)

In both equations local equilibrium is assumed according to the relationship:

\[ n_{i,j} = n_{i,j}^{eq}(c) \] (4.5)

The net flux of the species \( i \) in section \( j \):

\[ f_{i,j} = Q_s(1 - e_p)(m_j c_{i,j} - n_{i,j}) \] (4.6)

depends on the flow rate ratio \( m_j \) (cf. Eq (4.2)).

In order to achieve complete separation, i.e. to collect the more retained component A pure in the extract and the less retained component B pure in the raffinate, the unit must behave as described in section 1.1. Thus, the following conditions for the net fluxes (4.6) must be fulfilled:

\[ f_{A,1} > 0 \quad f_{B,1} > 0 \]
\[ f_{A,2} < 0 \quad f_{B,2} > 0 \]
\[ f_{A,3} < 0 \quad f_{B,3} > 0 \]
\[ f_{A,4} < 0 \quad f_{B,4} < 0 \] (4.7)

By using equation (4.6), these inequalities can be expressed as constraints on the \( m_j \) parameters:
\[ m_1 > \frac{n_{A,1}}{c_{A,1}}, \quad m_1 > \frac{n_{B,1}}{c_{B,1}} \]
\[ \frac{n_{B,1}}{c_{B,1}} < m_2 < \frac{n_{A,2}}{c_{A,2}} \]
\[ \frac{n_{B,1}}{c_{B,1}} < m_2 < \frac{n_{A,2}}{c_{A,2}} \]
\[ m_4 < \frac{n_{A,4}}{c_{A,4}}, \quad m_4 < \frac{n_{B,4}}{c_{B,4}} \]  

(4.8)

It is worth noting that the concentrations considered in these inequalities are those reached at steady state and therefore they are a function of the operating parameters \(m_j\). Thus, constraints (4.8) are at this stage implicit. By imposing the constraints (4.8) one can define the region of complete separation in the space spanned by the four coordinates \(m_1, m_2, m_3, m_4\).

When the feed mixture is infinitely diluted in the components to be separated the actual isotherm approaches the linear isotherm:

\[ n_i = H_i c_i \quad (i = A, B) \]  

(4.9)

where \(H_i\) is the so-called Henry constant of component \(i\). In these conditions the constraints on the \(m_j\) parameters reduce to the following set of decoupled inequalities (cf. (Ruthven, 1989)):

\[ m_1 > H_A \]
\[ H_B < m_2 < H_A \]
\[ H_B < m_3 < H_A \]
\[ m_4 < H_B \]  

(4.10)

In this case the complete separation region is a square triangle, as represented in Fig 4.1. It can be shown that in the region above the complete separation region only pure extract is obtained, while the raffinate is not pure. On the other hand, in the region to the left-hand side only pure raffinate is predicted, while the extract is impure.
FIG. 4.1: Regions of the \((m_2, m_3)\) plane leading to different separation regimes

With higher concentrations, the non-linearity of the isotherm must be taken into account. The constraints of the complete separation region in the \((m_2, m_3)\) plane have been calculated for several non-linear isotherm models under the assumption that the mobile phase is not compressible (see e.g. (Storti, 1993), (Migliorini, 1998)): in all cases the complete separation region is deformed with respect to the linear case and, when the isotherm is convex and the interaction between the eluent and the stationary phase is weak, the vertex is shifted towards the bottom left-hand corner of the \((m_2, m_3)\) plane. The pure extract region and the pure raffinate region are also deformed accordingly and in particular, the pure extract region becomes larger, while the pure raffinate region shrinks together with the complete separation region. What is more, the larger the feed concentration the stronger is this deformation. This effect is shown in Fig 4.2, where it is seen that, whatever the feed concentration, the basis of the complete separation region on the diagonal of the
The experimental refinement of these starting values can be performed efficiently by running few experiments, differing only in the switch time. In this way the corresponding operating points in the \((m_2, m_3)\) plane all lie on the same line: the values should be chosen in order to cross the complete separation region and to identify its size. In practice, of course, the size of complete separation region depends on the adopte purity constraints. Therefore, if the resulting optimal purity is above the requirements, it is possible to increase the throughput of the unit by increasing the feed flow rate, thus shifting the line
identified by the operating points further from the diagonal of the \((m_2, m_3)\) plane (the between \(m_3\) and \(m_2\) is proportional to the feed flow rate). In this way the performance of the SMB can be optimized “on the field” with very little knowledge of the system: just the Henry constants.

### 4.2 Adsorption isotherm models

In the case of low fluid phase concentration of the components to be separated, the adsorption equilibria under supercritical conditions can still be described by the linear relationship Eq (4.9). However, in this case, the coefficient \(H_i\) depends on density and this relationship can be empirically accounted for according to (van Wasen, 1975) as follows (cf. section 1.2):

\[
H_i = H_{i0}^0 \left( \frac{\rho}{\rho^0} \right)^{b_i} \quad (i = A, B) \tag{4.11}
\]

where \(H_i\) and \(H_{i0}^0\) are the Henry constants of component \(i\) at the operating and reference densities \(\rho\) and \(\rho^0\), respectively, and \(b_i\) is an empirical coefficient specific for the fluid and solid phase of equilibrium, which depends upon temperature.

The addition to the eluent of a modifier, e.g. a polar alcohol to supercritical carbon dioxide, results in a reduction of the Henry constant. Although in general the functional dependence of \(H_i\) on the modifier concentration, \(c_m\), can be rather complex, in the following analysis we will adopt the simplified relation (Lochmüller, 1989):

\[
\frac{1}{H_i} = a_i c_m + d_i \quad (i = A, B) \tag{4.12}
\]

where \(c_m\) is the modifier concentration and \(a_i\) and \(d_i\) are two empirical constants, which depend on the chromatographic system considered. Thus, in order to account for the effect of both density and modifier concentration on the Henry constant, we use Eq (4.12) to express the Henry constant at the reference density, \(H_{i0}^0\), and substitute it into Eq (4.11).

The resulting expression for \(H_i\) as a function of both \(\rho\) and \(c_m\) is:
In the following we will also use Eq (4.11) in the form:

$$n_{i,j} = H_{i,j} * w_{i,j} \quad (i = A, B \quad j = 1, \ldots, 4)$$

(4.14)

where $j$ indicates the SMB section, $w_{i,j}$ is the weight fraction and

$$H_{i,j} * = H_j \rho_j$$

(4.15)

where $\rho_j$ is the fluid density in section $j$.

As mentioned above, increasing the fluid phase concentration value leads to nonlinear competitive adsorption equilibria. The simplest effective model to describe this behavior is the classical Langmuir isotherm:

$$n_{i,j} = \frac{N_i K_i c_{i,j}}{1 + \sum_l K_l c_{i,j}} = \frac{N_i K_{i,j} * w_{i,j}}{1 + \sum_l K_{i,j} * w_{i,j}} \quad (i = A, B \quad j = 1, \ldots, 4)$$

(4.16)

where $K_{i,j} * = K_i \rho_j$, while $N_i$ and $K_i$ indicate the loading capacity and the equilibrium constant, respectively. Note that, in the limit of small fluid phase concentrations, the Langmuir isotherm approaches the linear isotherm, where $H_i = N_i K_i$.

It is worth noting that the adsorption models presented in this section do not take explicitly into account the competition of the solvent, though this may represent one of the main reasons of the effect of the total pressure on the adsorption isotherms under supercritical conditions (cf. Chapter 2 and 3). The simplest model to represent the competition of the solvent is the Langmuir model:

$$n_i = \frac{H_i c_i}{1 + K_s c_s + K_i c_i}$$

(4.17)
where the subscript \( s \) refers to the solvent (e.g. carbon dioxide). Let us now focus on the limit of infinite dilution of the solute, i.e. \( c_i / c_s \ll 1 \). In this case Eq (4.17) reduces to:

\[
 n_i = \left( \frac{H_i}{1 + K_i c_s} \right) c_i = H_i(p) c_i
\]  

(4.18)

where the apparent Henry constant can be expressed as a function of the solvent concentration and therefore of the fluid density. However, the dependence of Henry constant obtained with this model does not agree with the experimental data. Therefore we prefered to use the empirical model of Eq (4.11).

### 4.3 Conceptual description and modeling of an SF-SMB unit

The pressurization and depressurization dynamics after valve and column switch is of key importance for an SF-SMB unit operated in the pressure gradient mode. In fact, it affects both the adsorption fronts’ position and the mass balances. Furthermore, only when this phenomenon is properly taken into account, consistent equivalence relationships between the SF-SMB and the SF-TMB units can be established and the design criteria derived for the SF-TMB unit can be applied to the SF-SMB.

#### 4.3.1 SF-SMB operation

The goal of this section is to give a detailed description of the operation of the SF-SMB unit, focusing in particular on the pressurization/depressurization stage that occurs at the beginning of each time period after valve switch.

Let us consider the SF-SMB unit in Fig. 1.1, when operating in the pressure gradient mode. Each section \( j \) is in general constituted of \( n_j \) chromatographic columns and it is kept at a pressure \( P_j \), with \( P_1 \geq P_2 \geq P_3 \geq P_4 \) and accordingly \( \rho_1 \geq \rho_2 \geq \rho_3 \geq \rho_4 \). Obviously the isocratic mode can be regarded as a specific case of the pressure gradient mode defined above, where all pressure levels are the same. As shown in Fig 4.3, each node between
two columns is connected to the five inlets and outlets through on-off valves, while an an-
alogue valve acts as a back-pressure regulator, keeping the pressure in the upstream col-
umn at the set-point level.

After a switch, one column leaves and a new column enters each section. The column that
enters section $j$ must be pressurized from pressure $P_{j-1}$ to pressure $P_j$ for $j=1$ to 3, while
in section four it must be depressurized from $P_j$ to $P_4$. Since beside the back-pressure reg-
ulators four mass flow-meters and controllers are installed on the Feed, Extract, Raffinate
and Recycle flows, pressurization of section 1, 2 and 3 and depressurization of section 4
are made possible by feeding more eluent in section 1 and by removing more fluid from
section 4, respectively (Clavier, 1996). It is worth noting that the four flowrate set points
defined above, i.e. $E, F, R$ and $G_4$, determine a set of nominal internal flowrates $G_j$, giv-
en by: $G_3 = G_4 + R$, $G_2 = G_3 - F$, $G_1 = G_2 + E$. It is rather straightforward that the
mass of eluent to pressurize the first three sections and that to be removed from section 4
are exactly the same and equal to $V \varepsilon (\rho_1 - \rho_4)$, being $V$ and $\varepsilon$ the volume and the void
fraction of the column respectively. This proves that also during the initial pressurization/
depressurization stage of the time period between two valve switches the overall material
balance is fulfilled, despite the initial flowrates differ from the nominal ones. Therefore,
the additional mass to be fed to each section of the unit during pressurization/depressuri-
zation stage is simply $V \varepsilon (\rho_j - \rho_4)$ ($j=1,...,4$).
Considering that a typical Recycle flowrate is of about 5 Kg/h (Clavier, 1996) and the mass to be discharged, for a column of εf=0.1 L and Δρ =100 g/L, is usually less than 10 g, the equilibration time is about a few seconds. Similar considerations apply to the pressurization of the first three sections. Therefore in the following we will assume that the equilibration time is negligible in comparison to the switch time t*. According to this assumption, the average flowrate in section j over the time t*, \( G_j \), which is normally in the order of at least one minute, is given by:

\[
\overline{G_j} = G_j + \frac{V_e (\rho_j - \rho_f)}{t_{eq}} \quad (j = 1 \ldots 4)
\]

### 4.3.2 Dynamics of the adsorption fronts

In the following the pressurization effect on the dynamics of the adsorption front will be analysed, thus showing that it is always very small. Therefore the retention times of the two solutes in the unit can be evaluated with reference to the nominal flowrates, thus neglecting the pressurization contribution. However, the pressurization stream must be taken into account when defining the equivalence conditions between SF-TMB and SF-SMB because only thus the mass balances are fulfilled, as it will be discussed in section 3.3.

Let us consider for the sake of simplicity a single chromatographic column at a density \( \rho_2 \), where no solute is present. At time \( t=0 \) a stream at a higher density level \( \rho_1 \) enters the column, where the solute is at a concentration where linear adsorption isotherm with Henry constant, \( H \), applies. Before the column is equilibrated at the higher pressure value \( \rho_1 \), i.e. during the time period \( 0 < t < t_{eq} \), flowrate \( V_e \frac{\rho_1 - \rho_2}{t_{eq}} \) goes through it in addition to the nominal flowrate \( G \). For the sake of simplicity, instead of considering the rigorous fluiddynamic analysis, where the evolution of the density in the column from \( \rho_2 \) to \( \rho_1 \) is taken into account, two limiting cases are analysed, i.e. when the whole column is assumed to be already at the final density \( \rho_1 \) during the whole equilibration time (case A) and when the column is assumed to remain at the initial density \( \rho_2 \) during the whole equilibration time (case B), respectively. It is rather clear that the real behavior will be somehow intermediate between these two extremes. In the following, the variation of the retention time of the solute, due to the additional pressurization contribution, with respect to the case
where the initial density in the column is the same as that of the feed, i.e. \( \rho_2 = \rho_1 \), is shown to be negligible in both cases.

The end of the column of length \( L \) and cross sectional area \( S \) is reached at time \( t_R \), which is implicitly given in the first case A by:

\[
L = \left( \frac{G + V \varepsilon (\rho_1 - \rho_2)}{\varepsilon S \rho_1} t_{eq} + \frac{G}{\varepsilon S \rho_1} (t_R^A - t_{eq}) \right) \cdot \frac{\varepsilon}{\varepsilon + (1 - \varepsilon) H} \tag{4.20}
\]

and in the second case B by:

\[
L = \left( \frac{G + V \varepsilon (\rho_1 - \rho_2)}{\varepsilon S \rho_2} t_{eq} + \frac{G}{\varepsilon S \rho_1} (t_R^B - t_{eq}) \right) \cdot \frac{\varepsilon}{\varepsilon + (1 - \varepsilon) H} \tag{4.21}
\]

It is worth noting that the Henry constant \( H \) does not change in Eqs (4.20) and (4.21). Eq (4.20) yields:

\[
t_R^A = t_R^{ISO} - \frac{V \varepsilon}{G} (\rho_1 - \rho_2) \tag{4.22}
\]

while on the other hand Eq (4.21) leads to:

\[
t_R^B = t_R^{ISO} - \left( \frac{\rho_1}{\rho_2} - 1 \right) \left( \frac{V \varepsilon}{G} \rho_1 + t_{eq} \right) \tag{4.23}
\]

where \( t_R^{ISO} \) represents the retention time observed when the column is initially at the same density of the feed, i.e. \( \rho_2 = \rho_1 \), which is given by:

\[
t_R^{ISO} = \frac{V \varepsilon \rho_1}{G} \left( 1 + \frac{1 - \varepsilon}{\varepsilon} H \right) \tag{4.24}
\]
In order to evaluate the relative importance of the variation between \( t_R^{SO} \) and either \( t_R^A \) or \( t_R^B \), we consider some typical values of the operating parameters, namely a column volume \( V=0.2 \) L and a bed void fraction \( \varepsilon=0.4 \), where \( G=70 \) g/min, \( \rho_1 = 850 \) g/L and \( \rho_2 = 750 \) g/L (these correspond to \( P_1 = 210 \) bar and \( P_2 = 132 \) bar in the case of carbon dioxide at \( T=40 \) °C). Likewise in section 3.1, we will also assume that the equilibration time, \( t_{eq} \), is negligible when compared to the retention time in Eq (4.23). It can be readily calculated from Eqs (4.22) to (4.24) that \( t_R^A \) and \( t_R^B \) differ from \( t_R^{SO} \) by 1.7% and 2.1%, respectively. In the following we will neglect this pressurization effect when considering the adsorption front and always use Eq (4.24) to evaluate the retention time of a solute in the column.

### 4.3.3 TMB-SMB equivalence

Let us now determine the conversion rules that identify the flowrates of the SF-TMB unit that is equivalent to the SF-SMB unit described above. The former unit can be used to design the operating conditions of the latter, since they achieve in principle the same separation performance.

Let us consider the four sections of the SF-SMB and a reference point located at the beginning of the first column of each section (cf. (Migliorini, 1999b) for a similar analysis of the TMB/SMB equivalence problem). The fluid flowrate of the equivalent countercurrent SF-SMB unit is made of two different contributions: a positive contribution corresponding to the average SF-SMB flowrate given by Eq (4.19) and a negative contribution caused by the discrete jump of the whole column to the left of the reference point, occurring at the switch of the port positions and corresponding to an amount in mass equal to \( V\varepsilon\rho_j \). The latter must also be averaged over the whole period \( t^* \), thus yielding:

\[
G_{j}^{TMB} = G_{j}^{SMB} + \frac{V\varepsilon(\rho_j - \rho_4)}{t^*} - \frac{V\varepsilon\rho_j}{t^*} \quad (j = 1, \ldots, 4)
\]

which can be simplified to:

\[
G_{j}^{TMB} = G_{j}^{SMB} - \frac{V\varepsilon\rho_4}{t^*} \quad (j = 1, \ldots, 4)
\]
The continuous solid volume flowrate of the SF-TMB is given by the following relationship, i.e. by calculating the average solid flowrate in the SMB with respect to the same fixed reference point used before (Ruthven, 1989):

\[ Q_s = \frac{V(1 - \varepsilon)}{t^*} \]  

(4.27)

where \( Q_s \) is the TMB solid flowrate. Eqs (4.26) and (4.27) define an SF-TMB unit equivalent to the SF-SMB, i.e. a unit that achieves the same separation performance of the SF-SMB unit of interest (Storti, 1993). It is worth noting Eq (4.27) is the same as for the liquid case (cf.

### 4.4 Design of complete separation operating conditions

Let us consider a binary separation in a SF-TMB unit and let us assume that there are no mass transfer limitations and no axial dispersion (equilibrium theory model) and that the pressure drop in the columns is negligible, i.e. the density in each section is constant. Pressure as well density may change from section to section in the pressure gradient mode case.

The mass balance for the \( i \)-th component in the \( j \)-th section can be written as:

\[
\frac{\partial (\varepsilon^j W_{i,j} + (1 - \varepsilon) \omega_{i,j})}{\partial t} + \frac{\partial (G^j_{MB} W_{i,j} - Q_s n_{i,j})}{S \partial z} = 0
\]  

(4.28)

where \( t \) is the time and \( z \) the axial coordinate. It is worth noting that Eq (4.28) is the same as Eq (4.3), but it is more conveniently rewritten in terms of mass flowrate that remain constant when the density changes, in contrast to what happens for the volumetric flow-rates. Furthermore here the solid particles are assumed to be non porous. The adsorbed phase concentration, \( n_{i,j} \), is given in terms of the fluid phase compositions through one of the adsorption isotherms discussed above (cf. Eq (4.5))
The steady state solution of Eq (4.28) depends on the adsorption isotherm and on the flow-rate ratio $G_j^{TMB}/Q_s$ (Mazzotti, 1997b), which can also be expressed as a function of the SMB parameters using Eq (4.26):

$$m_j = \frac{G_j^{TMB}}{Q_s} = \frac{G_j^{SMB}}{V} \frac{t^* - V \rho_4}{(1 - \varepsilon)} \quad (j = 1, ..., 4) \quad (4.29)$$

The SMB design strategy adopted is the same as for incompressible eluents (cf. (Mazzotti, 1997b)): first optimal operating conditions to achieve the desired separation performance, i.e. complete separation of A and B in this case, for the SF-TMB unit are determined in terms of $m_j$ values; then these are converted into SMB operating parameters using Eq (4.29). In the case of an existing SF-SMB operated in pressure gradient mode nine parameters have to be selected, i.e. $G_j^{SMB}$, $\rho_j$, with $j=1, ..., 4$ and $t^*$. The switch time is in general selected based on column efficiency considerations, which for the sake of simplicity are omitted here since they have already been discussed elsewhere (Migliorini, 1999a), (Birresi, 2000).

### 4.4.1 Linear systems

Substituting Eq (4.14) and Eq (4.29), Eq (4.28) can be recast as:

$$\left(\varepsilon \rho_j + (1 - \varepsilon) H_{i,j}^* \right) \frac{\partial w_{i,j}}{\partial t} + Q_{s_m} (m_j - H_{i,j}^*) \frac{\partial w_{i,j}}{\partial z} = 0 \quad (4.30)$$

To achieve complete separation in a TMB or an SMB unit the following necessary and sufficient conditions must be fulfilled:

$$H_{A,1}^* < m_1$$
$$H_{B,2}^* < m_2 < H_{A,2}^*$$
$$H_{B,3}^* < m_3 < H_{A,3}^*$$
$$m_4 < H_{B,4}^*$$

(4.31)
Let us focus on the two central sections of the unit. When the SF-SMB is operated in the pressure gradient mode, two qualitatively different situations may occur, depending on whether $H_{A,2}^* > H_{B,3}^*$ or $H_{A,2}^* < H_{B,3}^*$. The regions of separation for the former case are drawn for the sake of clarity in Fig 4.4; the corresponding diagram for the latter case has been reported elsewhere (Mazzotti, 1997a). It is worth noting that a dimensionless definition of $m_j$ was used in (Mazzotti, 1997a); however the equations derived there and Eq (21) are formally the same and similar considerations apply.

Operating points in region 1 of Fig 4.4 allow complete separation to be achieved, whereas only the extract is pure in region 2 and only the raffinate is pure in region 3. The two components to be separated distribute in the two outlet streams in region 4, whereas they flood the raffinate or the extract in region 5 or 6, respectively.

Let us now focus on regions 7, 8 and 9 and let us show that these are only an artifact of the linear equilibrium model. In particular, operating points within region 7 satisfy the condition $m_2 > H_{A,2}^*$, i.e. the extract is flooded by pure solvent and does not contain $A$,
and \( H_{B,3} < m_3 < H_{A,3} \), i.e. the raffinate stream contains pure B. This means that A is fed to the unit, but it cannot come out and keeps accumulating inside the columns. This conclusion is not realistic, but it is perfectly consistent with the linear equilibrium model, which implies that the concentration can increase indefinitely without reaching a saturation limit. In reality, at high concentration values, the adsorption equilibria should be described by a nonlinear model, in which the concentration of the adsorbed phase reaches a saturation. In this case the shape of the separation region changes and region 7 disappears, as it is discussed in the next section. It is worth noting that similar considerations apply to region 8, where component B should keep accumulating, and region 9, where both components should accumulate indefinitely within the unit. These regions are only an artifact of the linear equilibrium model and do not exist in reality.

4.4.2 Nonlinear systems

Let us consider the general case in which a nonlinear adsorption equilibrium is established between the adsorbed and the fluid phase, which is described by the Langmuir isotherm (4.16).

The constraint on the flowrate ratio \( m_1 \) is the same as in the linear case, i.e. \( m_1 > H_{A,1} \), whereas that on \( m_4 \) is a function of \( m_2 \) and \( m_3 \), which can be rather complex (Mazzotti, 1997b) but also relatively easily dealt with in practical conditions. If a proper value of \( G_{4}^{SMB} \) cannot be found a priori, one can operate the SMB unit either with only three sections, i.e. collecting as the raffinate the whole flow from section 3, or in an open-loop configuration, i.e. collecting the stream from section 4 and checking its B content before recycling it to section 1. Both solutions are rather convenient, particularly when using a supercritical eluent.

Therefore in the following we focus on sections 2 and 3 of the unit and assume that the proper constraints on \( m_1 \) and \( m_4 \) are fulfilled, i.e. with reference to Fig 1.1 no component A is still adsorbed on the stationary phase after regeneration in section 1 and no component B is still carried by the mobile phase at the outlet of section 4. The material balances for the components A and B, in a control volume including the two central sections of the unit and assuming that complete separation is achieved, can be written as:
where $G_F$ is the feed flowrate, i.e.:

$$G_F = G_3^{TM} - G_2^{TM}$$  \hspace{1cm} (4.33)$$

Substituting Eq (4.29) into Eq (4.32) yields:

$$(m_3 - m_2)w_{A,F} + m_2w_{A,2} - n_{A,2} = 0$$  \hspace{1cm} (4.34)$$

$$(m_3 - m_2)w_{B,F} + m_3w_{B,3} - n_{B,3} = 0$$

Once coupled with Eq (4.16), Eq (4.34) is formally identical to what already reported elsewhere (Storti, 1993). In the isocratic case they are indeed identical and the same results presented previously can be applied. In the pressure gradient case, according to Eq (4.16) different isotherms in the different sections of the unit must be adopted. The derivation is conceptually similar to what reported previously (Mazzotti, 1997b), but more complex. For the sake of brevity here we do not report its mathematical details, since they are discussed elsewhere (Migliorini, 2000b). Following this procedure, the complete separation region for a binary system in the pressure gradient mode is obtained as a function of the isotherm parameters, the pressure levels in sections 2 and 3 of the unit and the feed composition.

In Fig 4.5 the complete separation region for the same model system but for different values of the overall feed weight fraction are drawn. It is worth noting that as in the incompressible, liquid case, the complete separation region becomes sharper and sharper as the feed concentration increases.
On the other hand the linear and nonlinear complete separation regions have different intersections with the diagonal; this is a peculiar feature of the SF-SMB operating in the pressure gradient mode that does not apply to the liquid SMB. Operating points close to the diagonal imply, in fact, small feed flowrate (compared to the flowrates in the unit). In liquid SMBs, this implies that the concentrations of the components to be separated within the unit are very small whatever the feed concentration. Therefore the conditions to achieve complete separation become the same as in the case of infinite dilution linear systems. On the contrary an SF-SMB unit operating in the pressure gradient mode, for operating points in region 8 of Fig 4.4, the concentration of component B builds up in section 3 and the linear conditions are never maintained, even for small feed flowrate (Migliorini, 2000b).
4.5 Analysis of performance and optimisation

The classical parameters used to evaluate the performance of SMB units are the desorbent requirement and the productivity per unit mass of stationary phase. Let us discuss these performance parameters as a function of the density levels in the unit and the modifier concentration.

4.5.1 Desorbent requirement

In an SF-SMB plant, carbon dioxide, i.e. the desorbent, is cooled down and pumped at low temperature to a certain pressure and then heated up to a supercritical state (Clavier, 1996). The operating cost is therefore almost independent of the final pressure that is reached by pumping a liquid. Therefore, the maximum pressure is established by the technical specifications of the plant and not by the operating costs. As a consequence the cost associated to the desorbent requirement, DR, is proportional to the amount of carbon dioxide fed per unit time to section 1. Since, until now, no economical study has been done about the relative importance of the energetic costs (cooling and pumping) in comparison to the CO₂ cost, it is difficult to establish a correct function for DR, when the CO₂ discharged from section 4 is actually recycled to section 1. In the following we will simply consider the total amount of CO₂ entering section 1, neglecting the recycling flowrate. This is given by its nominal value \( G_1 \) plus the amount needed for pressurization at each port switch. The minimum overall consumption is calculated using the minimum \( \phi_1 \) value from Eq (21) as:

\[
\bar{G}_{1,\text{min}} = \frac{V \rho_1}{\rho^*} (\varepsilon + (1 - \varepsilon) H_{11})
\]

Substituting Eq (4.13) one obtains:

\[
\bar{G}_{1,\text{min}} = \frac{V \rho_1}{\rho^*} \left( \varepsilon + \frac{1 - \varepsilon}{\rho_1} \frac{\rho_1^0}{\rho_1} \frac{d_1}{d_1} \right)
\]
For values of the parameters typical for supercritical chromatography where $b > 1$ this function is monotonically decreasing with $\rho_1$. Therefore unless other considerations apply, it is convenient to operate at the maximum allowable pressure in section 1.

On the other hand, Eq (4.36) shows that increasing the modifier concentration $c_m$ has always a positive effect on the desorbent requirement. This has to be paid by the necessity of recovering the modifier by the collected product streams.

### 4.5.2 Productivity

The productivity can be defined as following:

$$PR = \frac{w_F G_F}{M_{sp}}$$

where $w_F$ is the overall weight fraction of the solutes in the feed, $M_{sp}$ is the total mass of stationary phase and $G_F$ the feed flowrate that is given by $G_F = G_3^{SMB} - G_2^{SMB}$. Substituting Eq (4.29) yields:

$$PR = \frac{w_F V(1 - \varepsilon)}{t^* M_{sp}} (m_3 - m_2)$$

For a given switch time $t^*$, productivity is maximum on the vertex of the complete separation region where the distance from the diagonal is maximum. In the linear case, assuming $b_A = b_B = b$, and defining the selectivity $S_{AB} = \frac{H_A^s}{H_B^s}$, Eq (4.38) can be recast as:

$$PR^{opt} = \frac{w_F V(1 - \varepsilon) H_{B,3}^s}{t^* M_{sp}} \left( S_{AB} - \left( \frac{\rho_3}{\rho_2} \right)^{b-1} \right) = \frac{w_F V(1 - \varepsilon) H_{B,2}^s}{t^* M_{sp}} \left( S_{AB} \left( \frac{\rho_2}{\rho_3} \right)^{b-1} - 1 \right)$$

Assuming $b > 1$ and either $\rho_2$ or $\rho_3$ constant, the productivity is minimum in the isocratic mode, where $\rho_2 = \rho_3$ and increases as the pressure step between the two central sections of the unit increases. The pressure gradient mode improvement is larger for system of low selectivity, as it evident in Fig 4.6, where the ratio:
\[ \frac{PR_{PG_{opt}}}{PR_{ISO_{opt}}} = \frac{S_{AB} - \left( \frac{\rho_3}{\rho_2} \right)^b}{S_{AB} - 1} \]  \hspace{1cm} (4.40)

is plotted as a function of the system selectivity, assuming that the isocratic density is equal to \( \rho_3 \).

Let us now consider the effect of the modifier concentration. To our knowledge there are no data in the literature that show the effect of the modifier concentration on the nonlinear equilibria of a solute in supercritical carbon dioxide. Therefore we will focus on an SF-SMB unit operating under linear conditions. Furthermore no systematic study, in which both mobile phase density and modifier concentration were changed, has yet been reported. The addition of a modifier has in general two effects: first the the Henry constants be-
come smaller, secondly density changes less with pressure, i.e. the curve $\rho(P)$ is less steep. Therefore the productivity in both isocratic and pressure gradient mode will decrease and the beneficial effect of a pressure step between section 2 and 3 is less evident.

Let us consider the separation of chrysene and 1-metoxy-naphtalene on silica investigated at density equal to 0.6 g/cc (Lochmüller, 1989) and let us assume $b_A=b_B=3$ to describe the decrease of the Henry constants with density. Since the productivity is proportional to the distance from the diagonal of the operating point in the $(m_2, m_3)$ plane (cf. Eq (4.38)), we can see from Fig 4.7 that the productivity in the pressure gradient mode is always higher than in the isocratic mode, but it is lower at higher modifier concentrations. The maximisation of the productivity requires therefore a low modifier concentration, while the desorbent requirement is maximum in this case. All practical applications will therefore call for a compromise.

**Fig. 4.7:** Effect of modifier concentration for the system chrysene and 1-metoxy-naphtalene on silica. Distance from the diagonal of the optimal operating point in isocratic and pressure gradient mode.
4.6 Conclusion

The operation of the SF-SMB unit has been analyzed in detail and, based on proper simplifying assumptions, relationships that define an equivalent SF-TMB unit could be derived. This has allowed the “triangle theory” (Mazzotti, 1997b, Mazzotti, 1997a) to be extended to the SF-SMB operating in pressure gradient mode under nonlinear adsorption equilibria. Therefore, on the one hand, a powerful tool for the prediction of the separation performance and the choice of operating conditions of SF-SMBs is now available. On the other hand, a thorough analysis of the performance parameters (desorbent requirement and productivity) could be carried out and the process optimized. The pressure gradient operating mode shows always better performance than the isocratic mode particularly at low and very low selectivity, while a compromise in the choice of the modifier concentration is usually needed in order to match both productivity and desorbent requirements.
CHAPTER 5

Enantioseparation through SF-SMB chromatography

The majority of small scale liquid phase SMBs realizes the separation of chiral compounds (cf. Chapter 1). Therefore, the objective of this work has been to show the applicability of the SF-SMB technology to the separation of enantiomers, particularly of the enantiomers of the chiral pharmaceutical intermediate tetralol (1,2,3,4-tetrahydro-1-naphthol) whose chemical structure is given in Fig. 5.1.

![Chemical structure of tetralol](image)

**FIG. 5.1:** Chemical structure of tetralol. The position of the chiral center is indicated with an asterisk.
This enantioseparation is carried out on the chiral stationary phase ChiralcelOD (Daicel) using supercritical CO$_2$ modified with Ethanol as eluent in the SF-SMB pilot unit described in section 5.1. The design of the operating conditions that lead to the desired process specifications (i.e. complete separation of the two enantiomers) is based on the theoretical framework presented in Chapter 4 and requires information about the thermodynamics of the system, as discussed in sections 5.2 and 5.3. The results of the experimental runs are presented in section 5.4 and discussed in the light of the theoretical understanding of the SF-SMB behavior.

5.1 Experimental

5.1.1 Material and methods

Tetralol (1,2,3,4-tetrahydro-1-naphthol) was provided by Aldrich Chemical Company, USA. Carbon dioxide with a purity grade of 99% was obtained by Messer (France). Ethanol with purity of more than 99.8% was purchased by SDS (France).

5.1.2 SF-SMB experimental set-up

The SF-SMB unit available at the Novasep labs in Nancy (France) is constituted of eight columns (20 cm long with 3.3 cm internal diameter) arranged in a 2-2-2-2- configuration, i.e. two columns per section (see Fig. 1.2). In Fig 4.3 it is illustrated a scheme of the valve configuration between each pair of column ($C_n$ and $C_{n+1}$), which are connected by an on-off valve ($V_n$) and a back-pressure valve ($U_n$).

All the on-off valves are open except the one after the last column of section 4, whereas all the back-pressure valves are completely open in the isocratic mode and are used as control valves to allow for the desired pressure profile in the pressure gradient mode. Five on-off valves ($V_{jn}$, $j=1,\ldots,5$) connect each column to the two inlets (Eluent and Feed) and the three outlets (Extract, Raffinate and Recycling). Columns and lines are jacketed and kept at the desired temperature by a water bath.

The gaseous CO$_2$ from the cylinders is liquefied by cooling in a cryostatic bath, pumped to the desired pressure, and then heated up to the operating temperature. Four control
loops constituted of a mass flowmeter and a regulating valve are located at the Extract, Raffinate and Recycling outlets and at the Feed inlet in order to keep these flowrates at the set-point value. The Eluent flowrate attains automatically the value fulfilling the overall mass balance in the unit for the given pressure profile. It is worth noting that this control strategy, in which no constraints are imposed to the CO$_2$ source at the beginning of the unit, is particularly useful in the pressure gradient mode in order to shorten the time required to adjust the pressure levels in the different sections after the periodic switch of the inlet and outlet ports (cf. Chapter 4). The modifier is added through an HPLC pump to the Eluent. The solute, i.e. tetralol, is dissolved in Ethanol and added to the Feed inlet through a second HPLC pump.

Three cyclons connected in series are placed at the Extract, Raffinate and Recycling outlets and separate CO$_2$ from the modifier and the product that are collected at the bottom. The pressure in these separators is set between 40 and 60 bar and the temperature is chosen so that to keep them to operate in the two phase region of the ethanol-CO$_2$ system and with a minimum amount of organic modifier in the CO$_2$ reach phase. The ethanol-tetralol solution (in Extract and Raffinate) and the pure ethanol (in the Recycling) are periodically transferred to bottom separators at atmospheric pressure. Carbon dioxide is further purified through activated carbons and can in principle be recycled. However, since the modifier percentage is of key importance in determining the unit performance, only fresh CO$_2$ has been fed to the unit during all experimental runs.

The plant is completely automated and computer controlled. The safety of the plant is guaranteed both by electronic control, namely through high pressure and high temperature alarms and by safety valves and rupture disks properly located in different positions of the unit.

### 5.2 Retention and selectivity

The operating temperature has been chosen equal to 40 °C, since it is larger than the critical temperature of CO$_2$ (31 °C) and corresponds to the maximum operating temperature of Chiralcel OD. It is worth noting that, according to the estimated critical locus of the system CO$_2$-ethanol (Pöhler, 1997), the mixture is supercritical only up to a concentration of about 4.5% (w/w) of ethanol, i.e. for larger ethanol concentrations the critical temper-
ature is above 40 °C. Since in some of the pulse experiments and in all the SMB experiments a larger concentration of ethanol has been adopted, actually the eluent is a near-critical liquid at a temperature slightly below the critical one. Pulse experiments have been carried out in a supercritical fluid chromatograph using a UV detector with a high pressure cell (column length 25 cm, internal diameter 0.46 cm, overall bed void fraction $\varepsilon = 0.4$). In the following the most retained enantiomer will be indicated by A and the less retained one by B.

The Henry constants of the two enantiomers, i.e. the slope of the pure component adsorption isotherm at infinite dilution, have been measured at four different pressure levels (100, 150, 200, 250 bar) and modifier concentrations (1.9, 3.7, 5.4, 7.1% (w/w)). These have been calculated from the retention time of the maxima of highly diluted chromatographic pulses, under conditions where pressure drop in the column is negligible. As expected, it is found that the obtained Henry constants decrease when pressure and modifier concentration are increased, as shown in Fig. 5.3 for the more retained enantiomer. This is consistent with the observation that increasing pressure and ethanol concentration yields a larger solvation power and therefore a larger elution strength of the mobile phase.

In Fig. 5.4 these data are represented in a logarithmic plot as a function of the fluid phase density $\rho$, which is computed as a function of $T$, $P$ and ethanol content. The data can be interpolated for each component and at every modifier concentration level according to the relationship (van Wasen, 1975):

$$\ln H_i = a_i + b_i \ln \rho$$  \hspace{1cm} (5.1)

where $a_i$ and $b_i$ are system dependent dimensionless empirical coefficients which refer to the $i$-the component at a given modifier concentration and temperature, as reported in Table 5.1. It is worth noting that the same pressure levels correspond to different density values depending on the ethanol concentration.

The obtained data show that selectivity, defined as the ratio of the Henry constants of the two enantiomers, i.e. $S_{AB} = H_A/H_B$, is substantially independent of density. The values reported on the right hand side of the plot in Fig 5.3 show that selectivity decreases as the modifier concentration increases. Even though the absolute decrease is small, the impact on separation performance is strong since selectivity is very low, i.e. around 1.1.
FIG. 5.2: Henry constant of the more retained enantiomer of tetrinalol on ChiralcelOD at four different pressure (P, bar) and four modifier concentration levels (c_m weight %), as obtained by pulse experiments in the single column chromatograph. A similar behavior is exhibited by the less retained enantiomer (see Fig. 5.3)

<table>
<thead>
<tr>
<th>EtOH (w/w %)</th>
<th>b_A</th>
<th>a_A</th>
<th>b_B</th>
<th>a_B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>-3.33</td>
<td>24.8</td>
<td>-3.37</td>
<td>24.9</td>
</tr>
<tr>
<td>3.7</td>
<td>-2.98</td>
<td>22.0</td>
<td>-2.99</td>
<td>22.0</td>
</tr>
<tr>
<td>5.4</td>
<td>-2.73</td>
<td>20.0</td>
<td>-2.74</td>
<td>19.9</td>
</tr>
<tr>
<td>7.1</td>
<td>-2.61</td>
<td>19.0</td>
<td>-2.62</td>
<td>19.0</td>
</tr>
</tbody>
</table>

TABLE 5.1: Fitting parameters of the data in Figure 5.3 according to Eq (5.1).

5.3 Selection of the SF-SMB operating conditions

Adsorption equilibrium data presented in the previous section allow now the proper selection of the SF-SMB operating conditions, particularly with respect to the modifier concentration. On the one hand, the selectivity is larger and the separation is easier at low modifier concentration. In addition, low modifier concentration implies large values for
Enantioseparation through SF-SMB chromatography

the coefficients $b_i$ in Eq (5.1). which is advantageous since $b_i$ is a measure of the sensitivity of the Henry constant to pressure (density) changes. Therefore larger $b_i$ values lead to a more efficient pressure gradient operation mode. On the other hand, at low modifier concentration the Henry constants are large leading to large flowrates in section 1 to regenerate the adsorbent. Therefore there clearly exists an optimal situation, which in this case is heuristically established to correspond to a modifier concentration of 5.4% (w/w).

All the experiments were conducted at a relatively small feed concentration, i.e. 0.1 w% of each enantiomer, where the system approaches linear conditions. For the sake of simplicity only two pressure levels have been considered, i.e. 150 and 200 bar, corresponding to $\rho = 0.791$ and 0.845 kg/L, respectively. In the framework of the extension of the triangle theory to SF-SMB units operated both in the pressure gradient and in the isocratic modes (cf. Chapter 4), separation performance is controlled by the flow rate ratios, $m_i$, which have the dimensions of a density:
where $G_j$ is the mass flow rate in section $j$, $t^*$ is the switch time, $V$ the column volume and $\varepsilon$ the overall bed void fraction, i.e. $\varepsilon = 0.4$. In particular, in order to achieve complete separation it is seen that the following conditions have to be fulfilled:

\[
\begin{align*}
H_{A,1}^* &< m_1 \\
H_{B,2}^* &< m_2 < H_{A,2}^* \\
H_{B,3}^* &< m_3 < H_{A,3}^* \\
m_4 &< H_{B,4}^*
\end{align*}
\] (5.3)

where

\[
H_{i,j}^* = H_i \rho_j
\] (5.4)

The values of the parameters in the above equations used for the SMB runs are summarized in Table 5.2. These have been measured directly in the columns of the SMB unit after several hours of operation. It is worth noting that the absolute values of $H_A$ and $H_B$ in Table 5.2 differ from those reported in Fig 5.3, which refer to fresh adsorbent material. This seems to indicate some transient aging of the stationary phase, which however does not affect selectivity, whose value remains the same in the two sets of experiments.

From Eq (5.3) one can readily derive the region of complete separation in the ($m_2$, $m_3$) plane (cf. Chapter 4) for both isocratic and pressure gradient operation mode. These are shown for the case under examination in Fig 5.5: the two right triangles correspond to the isocratic operation at 150 and 200 bar, respectively, while the rectangle represents the complete separation region for the pressure gradient mode where sections one and two are kept at 200 bar and sections three and four at 150 bar. Since productivity is larger for operating points in the complete separation region which are further away from the diagonal, a rather clear advantage for the pressure gradient mode with respect to the isocratic mode is expected.
TABLE 5.2: Henry constants obtained by pulse experiments in the SMB unit

<table>
<thead>
<tr>
<th>P [bar]</th>
<th>ρ [kg/L]</th>
<th>H₀ [-]</th>
<th>H₁ [-]</th>
<th>H°₀ [kg/L]</th>
<th>H°₁ [kg/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>0.791</td>
<td>4.72</td>
<td>5.22</td>
<td>3.73</td>
<td>4.13</td>
</tr>
<tr>
<td>200</td>
<td>0.845</td>
<td>3.81</td>
<td>4.23</td>
<td>3.22</td>
<td>3.57</td>
</tr>
</tbody>
</table>

In Fig 5.4 the linear complete separation regions in the \((m_2, m_3)\) plane, corresponding to

isocratic mode operation at 150 and 200 bar (right triangles) are drawn together with the complete separation region for the pressure gradient mode where sections one and two are kept at 200 bar and sections three and four are at 150 bar. Since productivity is larger for
operating points in the complete separation region, which are further away from the diagonal, the theory predicts a rather clear advantage for the pressure gradient mode with respect to the isocratic mode.

5.4 Results and discussion

The experimental analysis has been designed so as to investigate the unit behavior in the same conditions considered in Fig 5.4, i.e. isocratic mode operation at 200 bar and pressure gradient mode operation at 200 bar in sections 1 and 2 and 150 bar in sections 3 and 4. In order to identify the location of the experimental complete separation region, the set of experimental runs summarized in Table 5.3 has been performed. In particular, for each operating mode, three sets of experimental runs at different feed flow rates have been carried out by changing only the switch time. As illustrated in Fig 5.4, each of such sets of experimental runs corresponds to a straight line almost parallel to the diagonal in the \((m_2, m_3)\) plane. This strategy allows the region of complete separation to be located, since it is expected that along such a line the operating point is initially in the pure raffinate region, goes through the complete separation region, and ends up in the pure extract region. The flowrate and \(m_j\) values, the switch time and the obtained purities in the Raffinate and in the Extract are reported in Table 5.3 for all performed experimental runs.
### TABLE 5.3: Summary of the SMB runs. The last two columns represent the purity reached in each run in the Extract and Raffinate stream, respectively.

<table>
<thead>
<tr>
<th>Mode</th>
<th>Feed [Kg/h]</th>
<th>G_f [Kg/h]</th>
<th>t* [s]</th>
<th>m_i [kg/L]</th>
<th>m_c [kg/L]</th>
<th>m_r [kg/L]</th>
<th>P_E [%]</th>
<th>P_R [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM Extr=1.0 kg/h</td>
<td>0.2</td>
<td>5.8</td>
<td>280</td>
<td>3.86</td>
<td>3.10</td>
<td>3.25</td>
<td>2.49</td>
<td>96.7</td>
</tr>
<tr>
<td>Raff=1.0 kg/h</td>
<td>0.3</td>
<td>5.7</td>
<td>295</td>
<td>4.02</td>
<td>3.21</td>
<td>3.45</td>
<td>2.65</td>
<td>97.2</td>
</tr>
<tr>
<td>Rec=4.0 kg/h</td>
<td>0.4</td>
<td>5.6</td>
<td>295</td>
<td>3.94</td>
<td>3.13</td>
<td>3.45</td>
<td>2.65</td>
<td>98.1</td>
</tr>
<tr>
<td>PG Extr=2.0 kg/h</td>
<td>0.6</td>
<td>6.9</td>
<td>275</td>
<td>4.60</td>
<td>3.11</td>
<td>3.56</td>
<td>2.43</td>
<td>91.5</td>
</tr>
<tr>
<td>Raff=1.5 kg/h</td>
<td>0.8</td>
<td>6.7</td>
<td>280</td>
<td>4.55</td>
<td>3.02</td>
<td>3.63</td>
<td>2.49</td>
<td>75.0</td>
</tr>
<tr>
<td>Rec=4.0 kg/h</td>
<td>1.0</td>
<td>6.5</td>
<td>300</td>
<td>4.75</td>
<td>3.11</td>
<td>3.93</td>
<td>2.70</td>
<td>96.6</td>
</tr>
</tbody>
</table>

#### 5.4.1 Extract and Raffinate purity vs. switch time

From the data in Table 5.3 and represented in Fig 5.5 is seen that in all experiments the purities of Extract and Raffinate change as a function of switch time, $t^*$, for given flow-rates, in the direction predicted by the SMB triangle theory (Pedeferri, 1999).

In particular, the Raffinate purities either remain practically constant above 99% or decrease when increasing $t^*$, while the Extract purities increase with $t^*$, with two exceptions at large $t^*$: for $F= 0.2$ kg/h in the isocratic mode and $F= 0.6$ kg/h in the pressure gradient mode. This is probably due to analytical inaccuracies due to the fact that in these conditions almost the entire racemic feed to the SF-SMB is collected in the Raffinate (with $P_R$ between 52% and 64%). Therefore it is particularly difficult to collect the tetralol product in the Extract stream and to obtain an accurate analysis of its enantiomeric purity.
5.4.2 Complete separation conditions

If we assume complete separation to be achieved when \( P_E > 97\% \) and \( P_R > 99\% \) and represent the corresponding operating points with filled circles and squares, we obtain the \((m_2, m_3)\) parameter plane shown in Fig 5.4. Although this definition is arbitrary, it allows...
us to realize that the location of the operating points achieving complete separation is not quantitatively consistent with the linear predictions of triangle theory. It is therefore necessary to adopt a non linear description of the adsorption equilibria. The simplest approach is to use the following binary Langmuir isotherm:

\[ n_i = \frac{H_i c_i}{1 + K_A c_A + K_B c_B} \quad (i = A, B) \]  

(5.5)

where \( c_i \) and \( n_i \) are the fluid and adsorbed phase concentration of component \( i \), respectively.

The parameters \( H_i \) are the Henry constants, which are known from the linear pulse experiments, whereas the equilibrium constants \( K_i \) have been determined by fitting the SMB experimental purity values. This leads to \( K_A = 10.3 \) and \( K_B = 9.3 \) at 150 bar and \( K_A = 11.2 \) and \( K_B = 10.1 \) at 200 bar.

**FIG. 5.6:** Experimental points as in Fig 5.4. Nonlinear separation regions according to a Langmuir model in isocratic mode at 200 bar with \( k_A = 11.2 \) and \( k_B = 10.1 \) at 200 bar.
and $K_B = 10.1$ at 200 bar. The corresponding nonlinear complete separation regions for the two operating modes considered are compared with the experimental data in Fig 5.6 and Fig 5.7. It is seen that the isocratic region remains actually rather similar to the linear region in Fig 5.4, which is consistent with the fact that the feed to the SMB is rather diluted. For the pressure gradient mode, the complete separation region is instead remarkably changed. In particular, not only the comparison with the experimental data is now satisfactory, but also physical inconsistency observed for the linear case at low feed flowrate, i.e. the complete separation region does not touch the diagonal as discussed in Chapter 4, is now resolved. This finding confirms the necessity of accounting for the equilibrium nonlinearities when describing the behavior of SMB units (cf. (Migliorini, 1998)).
5.4.3 Productivity optimization

The maximum productivity that can be achieved in each operating modes while maintaining complete separation conditions has been sought by increasing the feed flow rate. Since in the runs with feed flowrate $F=0.4$ kg/h in the isocratic mode and 1 kg/h in the pressure gradient mode, complete separation could not be achieved, it is reasonable to conclude that the maximum feed flow rate in the isocratic mode is between 0.3 and 0.4 kg/h, whereas that in the pressure gradient mode is between 0.8 and 1 kg/h, i.e. from two to three times larger. This is well illustrated in Fig 5.6 and Fig 5.7, when recalling that the distance from the diagonal of an operating point is proportional to its corresponding feed flowrate. Also with this regard the theory predictions are consistent with the experimental results.

It is worth noting that the above findings demonstrates the high efficiency obtained when operating the unit in the pressure gradient mode, which is possible only when using a near-critical fluid as eluent. This is particularly significant for difficult separations, such as the one in this work where selectivity is as low as 1.1.

5.4.4 Dynamics behavior of the SF-SMB unit

Another important manifestation of the adsorption equilibria nonlinearity is the peculiar unit behavior during start-up, which has been observed in some of the runs in the pressure gradient operation mode, particularly at large values of the switch time. For example the first ten cycle operation have been monitored during the run at $F=0.6$ kg/h and $t^* =300$ s, whose steady-state operating point is in the region of complete separation under linear conditions (see Fig 5.4) and in the pure Extract region under nonlinear conditions (see Fig 5.7). It has been found that the purity of the Extract stream remains always slightly larger but very close to the final value reported in Table 5.3, i.e. 96.5%, while the purity in the Raffinate remains very high (>99%) for the first eight cycles and then suddenly drops to the steady-state value of 55.7% (see Table 5.3).

A similar behavior has been observed experimentally in a liquid phase SMB unit for xylenes separation [Ballanec, 1993 #446] and also has been reproduced with an appropriate mathematical model. Through similar simulations it can be seen that, in general for liquid phase SMBs, the time needed to reach steady-state conditions becomes longer, the closer the corresponding operating point is located to the boundaries of the complete separation.
region. In the case of the SF-SMB start-up experiment under consideration the diagrams in Fig 5.4 and Fig 5.7 allow for a rather convincing interpretation. The separation process experiences in fact two different regimes. Initially, after start-up, the solutes in the unit are very diluted and linear adsorption equilibria apply. Since under these conditions the operating point is within the linear complete separation region (see Fig 5.4), high purity is observed in both outlet streams. Later, after some cycles, the enantiomers accumulate in the adsorbed phase and their concentration increases, thus entering the nonlinear adsorption equilibrium region, where the complete separation region changes (see Fig 5.7) and the operating point ends up in the pure extract region. This transition explains the strong delay in the drop of the Raffinate purity observed experimentally. It is worth noting that the understanding of this type of behavior may be of importance when start-up optimization and process control are considered.

5.5 Concluding remarks

For the first time the separation of the enantiomers of a chiral species, namely the pharmaceutical intermediate tetralol, has been carried out in a SF-SMB unit, i.e. a SMB unit with supercritical CO₂ as eluent. To design operating conditions Triangle Theory, properly extended, has been used. In this way complete separation in both the isocratic and the pressure gradient mode has been achieved. The experimental results confirm what anticipated by the theory, namely that the pressure gradient mode allows much larger productivity to be achieved than the isocratic mode.

In order to further investigate the potential of SF-SMB units, let us compare the performance in the pressure gradient mode (where a high pressure value \(P_H\) is applied to the first two sections and a low pressure value \(P_L\) to the third and fourth sections) with the isocratic mode (where all sections operate at \(P_H\)). When considering linear adsorption equilibria, optimal operating points and identical feed composition, the productivity ratio for the two operation modes is given by (cf. Eq (4.38)):

\[
R_{PR} = \frac{H_{A,L}^* - H_{B,H}^*}{H_{A,H}^* - H_{B,H}^*}
\]  

(5.6)
where the subscript $L$ and $H$ indicate that the Henry constant has been evaluated at the low and high density value, respectively. In Fig 5.8, the productivity ratio for our system is plotted as a function of $\rho_L$, assuming $\varepsilon=0.4$. It can be readily observed that this value is about 3 for the conditions investigated experimentally ($P_H=200$ bar and $P_L=150$ bar, i.e. $\rho_H=0.845$ kg/L and $\rho_L=0.791$ kg/L), but it can increase to almost 6 when $\rho_L=0.7$ kg/L (i.e. $P_L=100$ bar that corresponds to a pressure change of 100 bar between the two central sections of the unit).

It is worth noting that a complete process optimization would require a deeper understanding of the adsorption equilibria under supercritical conditions. In particular, the nonlinear competitive adsorption behavior of both enantiomers should be known as a function of pressure, together with their solubility in supercritical CO$_2$. This would allow the pressure profile along the unit and the feed composition to be optimized simultaneously. This cannot be accomplished with the data available in this work, which nevertheless succeed in showing both theoretically and experimentally the potential of SF-SMB units for difficult separation processes, such as chiral separations.
**FIG. 5.8:** Productivity ratio under linear conditions as a function of the low density level ($\rho_L$) at constant value of the high density level $\rho_H = 0.845$ kg/L, that, at 40°C and with 5.4% of Ethanol, corresponds to a pressure of 200 bar.
The first objective of the present Chapter is to deepen the understanding of the influence of the operating conditions (temperature, pressure and flowrate) on the most important chromatographic parameters (i.e. retention, efficiency and pressure drop). In particular, since chromatographic processes are usually isotherm, we will focus on the dependence that the solvent properties show as a function of the pressure. The adsorption of phenenatrene on Lichrospher 100 RP-18 (Merck) using pure CO₂ as eluent has been chosen as model system to investigate the properties mentioned above.

When operating with small particle diameters or relatively high flowrates (as it happens in preparative applications), the pressure drop along the chromatographic column may be non negligible. Therefore, because of the significant dependence of the physo-chemical solvent properties on pressure mentioned above, the solvent parameters exhibit a variation along the column that must be measured and taken into account. It is worth noting that supercritical fluids have a much lower viscosity than the usual organic solvents. Therefore
pressure drop in HPLC is usually much higher than in SFC, but, since the liquids are almost incompressible, the density and all the other properties remain unchanged along the column. Several researchers have already addressed this issue both from a theoretical and an experimental point of view ((Schoenmakers, 1987), (Janssen, 1991), (Janssen, 1992), (Bouigeon, 1996), (Bartle K. D., 1989), (Li, 1997), (Järemo, 1994), (Berger, 1990b), (Berger, 1994)). Martire ((Martire, 1989), (Martire, 1991), (Zhang, 1992), (Poe, 1990)), assuming that the pressure drop can be represented by the Darcy’s law, has defined a “temporal average density” and he has derived expressions for the observed capacity factor and plate height for an SFC column with non-negligible pressure drop. Some authors (Janssen, 1991), (Janssen, 1992) have calculated the capacity factor and the plate height of an SFC column with non-negligible pressure drop using data obtained in the absence of pressure drop at different densities and integrating them according to the density profile in the column. In the present work, we will use a similar model to find the thermodynamic parameters that realize the best fitting of the experimental data obtained under different conditions of average density and density profile. This approach may be particularly useful when data in the absence of pressure drop are difficult to obtain.

### 6.1 Experimental

#### 6.1.1 Materials and methods

Carbon dioxide (99.995% pure) was obtained by Pangas (Switzerland). Toluene (purity > 99.7 %) and phenantrene (purity > 97%) were provided by Fluka (Switzerland). The chromatographic column is a Lichrospher 100 RP-18 (Merck, Darmstadt, Germany); length and internal diameter are 125 mm and 4 mm, respectively, whereas average particle size is 5 μm.

#### 6.1.2 Experimental set-up

A schematic of the supercritical fluid chromatograph used in this study is drawn in Fig 6.1. The pure carbon dioxide eluent is delivered by an Isco 260D syringe pump (Isco, Nebraska, USA) at constant flowrate, whereas the outlet pressure is controlled by a Jasco back pressure regulator (model BP-1580-81, Jasco, Japan). The pump cylinder is jacketed
and cooled by circulating water at 15 °C; the jacket is insulated by a thick foam layer in order to minimize temperature fluctuations that would decrease the flowrate accuracy. From the cylinder, CO₂ is pumped by an air-driven pump (Maximator, Amman-Technik AG, Switzerland) - its head is also in the cooling bath - through a cooling heat exchanger and then to the syringe pump. The injection valve and the chromatographic column are kept within a water bath that was at 65°C in all the measurements presented here. The injection valve is a Valco CI4W with an internal loop volume of 60 nL (Valco Instruments Co. Inc., Houston TX, USA) and actuated by an electrical motor. The CO₂ stream goes through a coil about 130 cm long also placed in the water bath before reaching the injection valve at the experimental temperature. On-line monitoring is realized by a Jasco UV detector (model UV-1570) equipped with an high pressure cell of 4 μL volume; the data acquisition system (Borwin) is also provided by Jasco and runs on a PC. The temperature values in the different parts of the plant are measured through temperature resistors Pt100 which have been previously calibrated with an accuracy of 0.1 K. The apparatus is equipped with two pressure sensors and a differential pressure sensor (see Fig 6.1). The pressure sensors are Trafag 8891 (Trafag AG, Switzerland) and have a specified accuracy of 0.4 bar. The differential pressure sensor is a Validyne DP15 (Validyne, Northridge CA, USA) and has an overall accuracy of 0.25 bar for measurements up to 50 bar. All these instruments have been calibrated against a calibration standard instrument (Huber, Switzerland) that has a specified accuracy of 0.03 bar.
6.1.3 Experimental procedure

After filling the syringe pump, about 20 minutes are allowed for thermal equilibration; then the pump is started and the pressure drop is monitored. When it reaches a stable value, i.e. the flowrate is constant and stable, the system is ready for injection. For each set of operating conditions, different solutions of phenantrene dissolved in toluene have been injected. The attainment of linear adsorption conditions has been verified by checking the invariance of the retention times for decreasing phenantrene concentrations, i.e. for decreasing amounts injected. Measurements have been repeated several times, thus proving a satisfactory reproducibility, with deviations in the retention times within 1% of the average value.

Let us now discuss the determination of the column void volume. The choice of an unretrained solute in chromatography is still an open issue. In fact, on the one hand, it should exhibit no interactions with the stationary phase, but, on the other hand, it should have shape and dimensions similar to the ones of the solute in order to access the same voids and pores as the solute molecule of interest. Therefore the use of small molecules like helium does not always solve the problem (Janssen, 1991). For the sake of simplicity, we
finally decided to inject toluene at the highest pressure allowed in the plant, i.e. where the retention should be minimum, and use its retention time for the estimation of the overall bed void fraction, estimated to be equal to 0.65.

For pressure drops up to 50 bar, the differential pressure read-out has been compared with the value obtained from the two pressure sensors. Although the agreement was always quite satisfactory with a maximum deviation of 7%, in the following only the differential pressure sensor read-out has been considered since it has a better accuracy. When the pressure drop exceeded 50 bar, the differential pressure sensor was not accurate anymore and the $\Delta P$ value obtained from the two pressure sensors has been used. The maximum absolute error of this measurement is expected to be about 0.8 bar; this corresponds to a relative error of about 1.6% at 50 bar pressure drop, which decreases when pressure drop increases. In order to evaluate separately the contribution of the column and of the lines to the overall pressure drop, a series of measurements has been carried out, under the same operating conditions of outlet pressure and flowrate, by substituting the column with a short capillary that yields a negligible contribution to the overall pressure drop. It has also been verified that the extra-column pressure drop is mostly due to the narrow tubes (0.12 mm of internal diameter) placed between the injection valve and the column (5 cm long), and between the column and the UV detector (8 cm long). Since the pressure drop is proportional to the length of the tube, it has been possible to separate the different contributions.

### 6.2 Results and discussion

#### 6.2.1 Pressure drop

Let us first consider the pressure drop measurements that are summarized in Table 6.1. These have been obtained at different values of the outlet pressure and of the volume flowrate, $Q_p$. It is worth noting that the mass flowrate, $G$, can be calculated since the density in the pump cylinder is known, being known its temperature (15 °C) and pressure. When the outlet pressure increases, the pressure drop in the lines decreases (see Fig 6.2), whereas the pressure drop in the column increases (see Fig 6.3).
TABLE 6.1: Pressure drop as at the four different outlet pressures, \( P_0 \), as a function of the pump flowrates, \( Q \). \( \Delta P_{bc} \) and \( \Delta P_{ac} \) represent the pressure drop in the tubes respectively before and after the column, while \( \Delta P_c \) is the pressure drop in the column.

<table>
<thead>
<tr>
<th>( Q ) [mL/min]</th>
<th>( P_0=110 ) bar</th>
<th>( P_0=130 ) bar</th>
<th>( P_0=180 ) bar</th>
<th>( P_0=220 ) bar</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.7</td>
<td>1.9</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>1</td>
<td>2.4</td>
<td>3.8</td>
<td>1.9</td>
<td>3.9</td>
</tr>
<tr>
<td>3</td>
<td>15.3</td>
<td>11.8</td>
<td>13.4</td>
<td>12.7</td>
</tr>
<tr>
<td>5</td>
<td>35.6</td>
<td>23.7</td>
<td>33.3</td>
<td>24.9</td>
</tr>
</tbody>
</table>

\( \Delta P_{bc} \) and \( \Delta P_{ac} \) are obtained using Eq (6.1) and \( \alpha = 1.5 \times 10^{12} \, \text{cm}^{-1/4} \).

Since the Reynolds number in the tubes of 0.12 mm inner diameter ranges between 1000 and 10000, pressure drop in the tubes according to the Blasius equation:
\[ \Delta P_{Blausius} = \int_0^{L_{tubes}} \left( \alpha \cdot \frac{G^{7/4} \mu^{1/4}}{\rho} \right) dz \]  \hspace{1cm} (6.1) 

where \( \mu \) and \( \rho \) are the CO\(_2\) viscosity and density respectively, \( \alpha \) is a geometrical parameter and \( L_{tubes} \) is the tubes length. The interpolating lines drawn in Fig 6.2 are obtained using Eq (6.1) and \( \alpha = 1.5 \times 10^{12} \text{ cm}^{-19/4} \); the units of the other quantities are given in the Notation. The data reported in Fig 6.2 refer to the tubing after the column and an analogous plot may be obtained for the tubing before the column. It has been verified, in fact, that the pressure profile along the tubes is linear as a function of the length. Hence 5/13 of the overall pressure drop pertains to the lines before the column and 8/13 of it to the lines after the column.

![Graph showing pressure drop vs. mass flowrate for different outlet pressures](image)

**FIG. 6.3:** Pressure drop in the column as a function of the mass flowrate for the four outlet pressures investigated. The symbols represent the experimental points, while the lines are fitting according to Eq (2), with \( \beta = 7.2 \times 10^{4} \text{ cm}^{-4} \) and \( \gamma = 2.7 \times 10^{3} \text{ cm}^{-5} \).

The pressure drop in the column can be described by the Ergun’s equation:
\[ \Delta P_{\text{Ergun}} = L \int_0^L \left( \beta \cdot \frac{G \mu}{\rho} + \gamma \cdot \frac{G^2}{\rho} \right) dz \]  

(6.2)

where \( \beta \) and \( \gamma \) are column geometrical parameters, which include particle size and porosity and \( L \) is the column length. The fitting has been carried out on all the experimental point presented in Table 6.1 with the exception of the values obtained at the two highest flowrates at \( P = 110 \) bar, since they will not be used in the analysis of the chromatographic results (see section 6.2.2). The fitting is rather satisfactory and the absolute deviation between calculated and experimental pressure values are always lower than 1 bar. The corresponding fitting parameters assume the values of \( \beta = 7.2 \times 10^4 \) cm\(^{-4}\) and \( \gamma = 2.7 \times 10^{-3} \) cm\(^{-5}\). It is worth noting that \( \mu \) and \( \rho \) must be evaluated at the local pressure value and vary along the integration path. The fluid density, \( \rho \), has been evaluated according to the Span and Wagner equation of state (Span, 1996), while \( \mu \) is evaluated according to a relationship proposed previously (Fenghour, 1998).

### 6.2.2 Retention times

The retention times of phenantrene at different pump flowrates, \( Q_p \), and different outlet pressures, \( P_o \), are reported in Table 6.2.

<table>
<thead>
<tr>
<th>( Q_p ) [mL/min]</th>
<th>( P_o = 110 ) bar</th>
<th>( P_o = 130 ) bar</th>
<th>( P_o = 180 ) bar</th>
<th>( P_o = 220 ) bar</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>( t_{R,\text{ex}} )</td>
<td>( t_{R,\text{calc}} )</td>
<td>( \text{err}% )</td>
<td>( t_{R,\text{ex}} )</td>
</tr>
<tr>
<td>1</td>
<td>104.6</td>
<td>106.0</td>
<td>-2.1</td>
<td>33.57</td>
</tr>
<tr>
<td>5</td>
<td>44.23</td>
<td>43.39</td>
<td>1.9</td>
<td>15.26</td>
</tr>
<tr>
<td>3</td>
<td>3.03</td>
<td>2.82</td>
<td>6.8</td>
<td>1.48</td>
</tr>
<tr>
<td>5</td>
<td>1.18</td>
<td>1.05</td>
<td>11.1</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**TABLE 6.2:** At each pressure level, in the first column indicated as \( t_{R,\text{ex}} \), the experimental retention times of phenantrene (in minutes) on Lichrospher 100 RP-18 are reported. The flowrates indicated in the Table are the ones delivered at the pump which was kept at 15 °C. The retention times calculated according to the model described in the text are reported in the second column, \( t_{R,\text{calc}} \), while the relative error is reported in the third column.
At $P_0 = 110$ bar, no measurements could be carried out at $Q_p = 3$ and 5 mL/min because the baseline noise exceeded the phenantrene peak.

Retention times exhibit the expected decrease when the CO$_2$ density is increased (Perrut, 1994). A widely used model to represent the variation of the Henry constant, $H$, with density is (van Wasen, 1975):

$$\ln H = a + b \ln \rho \quad (6.3)$$

where $a$ and $b$ are two system dependent parameters. If the density remained constant along the column, then the Henry constant would be simply related to the column void volume $\varepsilon$ and to the residence time of the solute, $t_R$, and of an unretained compound, $t_0$, as follows:

$$H_{obs} = \frac{t_R - t_0}{t_0} \cdot \frac{\varepsilon}{1 - \varepsilon} \quad (6.4)$$

When the density changes along the column, $H_{obs}$ represents an average value of the actual Henry constant $H$, which varies along the column length.

Therefore, it is possible to give a consistent interpretation to the experimental results only if the pressure profile along the column is taken into account. From the pressure drop measurements presented in the previous section, the density profile $\rho$ has been evaluated according to the Span and Wagner equation of state (Span, 1996). A dependence of the capacity factor on the local value of density according to Eq (6.3) has been assumed and the local solute velocity in the column has been calculated according to:

$$u_{sol}(\rho) = \frac{v(\rho)}{(\varepsilon + (1 - \varepsilon) \cdot H(\rho))} \quad (6.5)$$

where $u(\rho)$ is the local value of the mobile phase superficial velocity given by:

$$u(\rho) = \frac{G}{Sp} = \frac{Q_p}{S} \quad (6.6)$$
where $S$ is the column section. It is worth noting that a decreasing density gradient causes both the numerator and the denominator of Eq (6.5) to increase. However, in practical cases, the increase of the Henry constant always dominates since the coefficient $b$ in Eq (6.3) is always greater than one, while $v$ is simply inversely proportional to $\rho$. Therefore, most often the velocity $u_{sol}$ increases along the column. The retention time, $t_R$, may be evaluated from the following integral:

$$ t_R = \int_{0}^{L} \frac{1}{u_{sol}} dz \quad (6.7) $$

where $z$ is the axial coordinate.

The model has been used to fit the experimental data in Table 6.2, by minimizing the following objective function:

$$ F = \sum_{i} \left( \frac{t_{R_i} - t_{R_i,ex}}{t_{R_i,ex}} \right)^2 \quad (6.8) $$

where $t_{R_i}$ and $t_{R_i,ex}$ are respectively the calculated and the experimental retention time corresponding to the $i$-th run.

The values of the parameters $a$ and $b$ in Eq (6.3) that realize the best fitting have been found to be $a = 31.977$ and $b = 4.536$. The comparative plot in Fig 6.4 shows that the fitting is rather satisfactory. The calculated retention times are reported in Table 6.2, together with the relative error when compared to the experimental points. The average error is about 3% and the maximum error is 11.1%, which corresponds to the run at 130 bar at the highest flowrate. However, it is worth noting that in this case the absolute error is less than 8 sec.
The thermodynamic parameters have also been estimated plotting the observed averaged Henry constant (as given by Eq (6.4)) vs. the average temporal density (Zhang, 1992). The starting idea is that there exists always a value of the density that, substituted in Eq (6.3), leads to a value of the Henry constant equal to the observed one. Assuming that the Darcy’s law applies, it has been shown that the density averaged over the residence time in the column of an unretained solute (the so-called temporal average density) can be calculated if the only inlet and outlet density values are known, as follows:

$$
\langle \rho \rangle_t = \frac{\int_0^{t_0} \rho \, dt}{\int_0^{t_0} \, dt} = \frac{\rho_t \int_0^{t_0} \left( \frac{d\rho}{d\rho} \right)_t \, d\rho}{\rho_i \int_0^{t_0} \left( \frac{d\rho}{d\rho} \right)_t \, d\rho}
$$

(6.9)
Martire measured the Henry constant of ethylbenzene in sc-CO₂ on a silica column at different flow rates and therefore pressure drop values. He found that, when the observed capacity factors are plotted as a function of the temporal average density, they fall on the same curve (Zhang, 1992). It is worth noting that no theoretical explanation to this behavior has been found yet for this empirical observation. The observed Henry constants of our system have been plotted as a function of the temporal average density in Fig 6.5. As we can see, they fall on the same straight line whose slope and intercept are almost identical to the coefficients calculated with our approach where Eq (6.3) has been assumed, i.e. \( a = 31.347 \) and \( b = 4.524 \). Moreover, if the observed Henry constants are plotted as a function of the arithmetic density, the results are rather similar. In fact, in the case of temperatures rather far from the critical one, the density profile in the column becomes linear and all the averages lead to the same value. We can therefore conclude that, in this example, the approach proposed by Martire is compatible with our method. However, while our ap-
proach have a theoretical foundation, Martire’s one has not. Furthermore there is agreement between our and Martire’s approach until the Darcy’s law can give a rather good representation of the pressure profile. It is possible to show, in fact, that if the plot $\Delta P$ vs. $G$ shows a larger curvature, i.e. the second term on the r.h.s. of Eq (6.2) becomes more important, the results of our approach differ significantly from the ones obtained using Martire’s approach. Finally, since our approach does not rely on any empirical observation, it can be easily extended to nonlinear adsorption equilibria as discussed in the Conclusions of this chapter.

6.2.3 Efficiency

The efficiency of a chromatographic column can be expressed as the number of theoretical plates, $N$, which can be evaluated from the experimental chromatograms as:

$$N = 5.44 \left( \frac{I_{0}}{w} \right)^{2} \quad (6.10)$$

where $w$ is the width at half of the peak height [Le Van, 1997 #448]. The reproducibility of these measurements is not very good and the standard deviation reaches the values of 14 and 21% for the experiments at 5 mL/min at 220 and 180 bar, respectively. However, the uncertainty in the measurements does not invalidate the qualitative trends and the considerations that follow. The relation between efficiency and mobile phase velocity is usually represented by the van Deemter plot, in which the height of the theoretical plate, $HETP$, obtained dividing the length of the column by the number of plates, is plotted as a function of the column velocity. In the case of non-negligible pressure drop, the mobile phase velocity decreases along the column, as discussed in the previous section, and in Fig 6.6 we plot $HETP$ as a function of the mass flowrate, which remains constant along the column. The results are also presented in Table 6.3.

All the curves exhibit a minimum for values of $G$ of about 1 g/min, which correspond to the optimal flowrates for each pressure level. The minimum column efficiency is observed at the minimum pressure, then the efficiency increases when the pressure is increased to 130 and 180 bar. However the curve at 220 bar is higher than the one at 180
SFC with non-negligible pressure drop

<table>
<thead>
<tr>
<th>$Q_p$ [mL/min]</th>
<th>$P_o=110$ bar</th>
<th>$P_o=130$ bar</th>
<th>$P_o=180$ bar</th>
<th>$P_o=220$ bar</th>
</tr>
</thead>
<tbody>
<tr>
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<td>76.8</td>
<td>47.6</td>
<td>30.9</td>
<td>31.2</td>
</tr>
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<td>40.2</td>
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<td>20.7</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>60.8</td>
<td>23</td>
<td>34.9</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>47.4</td>
<td>51.4</td>
<td>65.9</td>
</tr>
</tbody>
</table>

TABLE 6.3: Hight of the theoretical plate (HETP) for the phenantrene peak (in $\mu$m). Same conditions as in Table 6.2.

bar, i.e. the efficiency seems to have a maximum and decreases when the pressure is further increased.

In the last 10 years, several works on this topic have been published and different opinions have been expressed about the effect of density and the role of pressure drop in determin-
ing the efficiency of an SFC column. Since many parameters interact at the same time, it is difficult to clearly rationalize experimental results that are sometimes contradictory. A decrease of the number of plates when increasing the density at constant temperature was also found by (Berger, 1990b), while an opposite behavior is reported by (Schmitz, 1987), (Köhler, 1994a), (Köhler, 1994b) and (Shah, 1990). Let us consider the van Deemter equation:

\[ HETP = A + B/u + Cu \]  \hspace{1cm} (6.11)

where:

\[ B = B'D_{12} \] \hspace{1cm} (6.12)

and

\[ C = \frac{C'}{D_{12}} + \frac{H}{(1+H)^2} \cdot C'' \] \hspace{1cm} (6.13)

where \( A, B', C', C'' \) are system dependent parameters, which do not depend on the operating conditions. \( D_{12} \) is the diffusion coefficient of the solute in CO₂ that is inversely proportional to the pure solvent’s viscosity and therefore decreases with increasing density (Sassiat, 1987). A decrease of density causes always an increase of \( B \) and a decrease of the first term in \( C \), while the second term of \( C \) increases when \( H>1 \) (as in our case) and decreases when \( H<1 \). It is therefore clear that a general rule about the behavior of \( HETP \) as a function of density cannot be derived and opposite trends for different systems are not surprising. The results shown in Fig 6.6 may also be strongly affected by the pressure drop. Schoenmakers and coworkers analyzed the behavior of both capillary and packed columns and concluded that pressure drop is detrimental for the efficiency when low density values are used ((Schoenmakers, 1987), (Janssen, 1991), (Janssen, 1992)). However, Berger showed that density differentials cannot be the direct cause of the loss in efficiency since he obtained that the same density differential produces very different efficiencies at different temperatures (Berger, 1990b). He suggested that the observed efficiency loss may arise from a loss in solubility. Bouigeon and other researchers observed again a de-
crease of the column efficiency when the density gradient increases, but their results were independent of temperature (Bouigeon, 1996). Moreover, they showed that the apparent efficiency was constant when injections at different density levels were done in a column with negligible pressure drop. This means that the mobile phase density was always large enough to solubilize the solute, but also that the effect of the density level on the efficiency was negligible, at least in the range of density and for the system investigated. In our system, from an estimation according to (Méndez-Santiago, 1999), the solubility of phenanthrene in CO₂ should not be a problem, even at the lowest experimental pressure of 110 bar, which correspond to a density of 320 g/L. Therefore, the fact that the curves in Fig 6.6 decrease when the density levels is decreased would be simply explained in terms of increasing density gradients. In fact, although the pressure drop increases with the outlet pressure, the density gradient is higher at lower pressure values, where the compressibility is higher. E.g., at 65°C, a pressure drop of 20 bar causes a density drop of 26 g/L when $P_o=220$ bar and of 129 g/L when $P_o=110$ bar.

### 6.3 Concluding remarks

A thorough analysis of the behavior of a SFC column with non-negligible pressure drop has been carried out, looking at the linear adsorption equilibria of phenanthrene on Lichrospher 100 RP-18 using pure carbon dioxide as eluent. It has been shown that a sound description of the thermodynamics of the system can be obtained only if the pressure profile of the column is taken into account. The procedure presented above allows the thermodynamic parameters to be determined as a function of density, when the following information is available: 1) linear chromatograms obtained under non-negligible pressure drop 2) pressure profile and 3) the fluid equation of state. This procedure can be easily extended to the case where nonlinear adsorption equilibria apply. In this case, it can be shown that the retention time is given by the same equation derived for the GC case (cf. (Juza, 1998)):

$$t_R(y) = \int_{0}^{1} \frac{L_\varepsilon + (1-\varepsilon)(1-y) \cdot \frac{dq}{dc} \cdot dz}{v}$$

(6.14)
where $y$ is the molar fraction of the solute and $v$ is given by Eq (6.6). An adsorption isotherm model and a dependence of the isotherm parameters on the density must be assumed. It is worth noting that both the velocity and the isotherm derivative vary along the integration path. By coupling Eq (6.14) and the mass balance of the solute peak, the retention time may be estimated if the adsorption isotherm and its dependence on the system density are known. On the other hand, if some overload chromatograms obtained under non-negligible pressure drop are available, the system thermodynamics can be determined through an optimization procedure as it has been shown in section 6.2.2 under linear conditions.

The thermodynamic characterization of the system represents the basis for the design of the optimal operating conditions both for batch and continuous chromatographic processes. However, the efficiency of the system must also be taken into account, but the behavior is in general more complex and difficult to model because many parameters are present at the same time. The only conclusion that may be drawn is that density gradients reduce in general the column efficiency and it should be avoided to operate too close to the critical point, where the fluid compressibility is very large, thus leading to very large density gradients even for small pressure drop. However, further work is needed to in this direction.
SFC with non-negligible pressure drop
In this Chapter the main results of this work are summarized and discussed in a critical perspective. In particular, objectives and directions for future work are presented.

The use of supercritical fluids as eluents in continuous chromatographic processes has been investigated, addressing both fundamental and applicative issues. SF-SMB is a new process, which not only combines the advantages of both SMBs and supercritical fluids but exhibits some further interesting peculiar features. The main feature of supercritical fluids is the tunability of their properties. With reference to chromatographic processes, the retention time of a solute may be tuned by changing the pressure of the eluent. This fact may be exploited to increase the performance of SF-SMBs by applying a decreasing pressure gradient along the four sections of the unit (pressure gradient mode, cf. section 1.3).

It is therefore clear that the adsorption thermodynamics under supercritical conditions is the key fundamental issue that must be addressed to exploit the whole potential of this
technology. In particular, only when we will have reached a sound understanding of the adsorption equilibria, we will be able to design a proper stationary phase and to choose the systems that are more suitable to be separated with this technique. Until now, in fact no adsorbents have been specifically designed for SFC and the instrumentation and the approaches adopted have been simply imported from liquid chromatography. The fundamental studies on the solvent adsorption isotherms (cf. Chapters 2 and 3) answer to this need and represent the first essential step towards a sound description of the adsorption of supercritical mixtures. It has been shown, comparing chromatographic systems using different eluents (of which the eluent adsorption isotherm was known), that, in some cases, nonidealities in the fluid phase are more important than the solvent competition in determining the decrease of the retention time with density (cf. section 3.3). Since this effect should be maximized (i.e. the coefficient $b$ in Eq (1.1) must be maximized) in order to optimize the beneficial effect of the pressure gradient mode in SF-SMBs, these fundamental studies should help in the choice of a system (adsorbent, supercritical solvent, modifier…) where fluid nonidealities (and eventually solvent competition) exhibit a large change with the pressure level. Therefore the big effort on this fundamental issues is not only justified by scientific and academic interest, but it has direct consequences on the development of SF-SMB technology. We strongly believe that the adsorption thermodynamics of supercritical fluids deserves further work in the future and the results obtained in these years should stimulate one to continue in this direction. Some guidelines and suggestions for the future work in this area are discussed in section 3.4 of this dissertation.

In this work, together with the fundamental studies on the adsorption thermodynamics, particular attention has been devoted to the SF-SMB process itself both from a theoretical and an experimental point of view. The main results of this work are presented in Chapters 4, 5 and 6.

In Chapter 4 proper design criteria has been derived in the frame of the triangle theory for a SF-SMB unit operating in pressure gradient mode both under linear and nonlinear adsorption equilibria. It has been shown that the unit performance is always higher when operating in pressure gradient mode (PG) compared to isocratic mode (ISO). In fact, the vertex of the complete separation region in PG mode is moved further away from the diagonal compared to the same system in ISO mode. Therefore, the productivity (which at constant feed concentration and switch time is proportional to the distance from the diag-
onal) is higher in the former case and the improvement is more evident when, for a given system, the pressure difference between the two central sections of the unit increases and when, at constant pressure difference, the system selectivity is lower. The PG mode is therefore more beneficial for difficult separation, i.e. for systems that exhibit very low selectivity.

The main assumptions that have been done in developing the theory are that the pressure drop along the columns is negligible and that the solid particle are nonporous. The issue related to pressure drop has been addressed in Chapter 6 for the linear case, where the separation criteria can be derived looking directly at the SMB unit. However, when non-linear equilibria apply, the theory must be developed for a TMB unit and then applied to SMBs using the equivalence relationships. These relationships are available for a SMB unit using liquid eluents (cf. Eq (4.1)) and for a SF-SMB unit in PG mode but with negligible pressure drop along the column (cf. Eqs (4.24) and (4.25)). When a pressure profile along the columns is established, the equivalence relationships are difficult to obtain and this remains an open issue also for GC-SMB (SMB using a gas as eluent (Juza, 1998)). In order to remove these two assumptions (negligible pressure drop and porosity of the solid) further work is required for the future.

A further objective for future work in the theoretical framework is the development of a detailed model of the unit in which not only the adsorption equilibria, but also axial dispersion and mass transfer resistances are taken into account. In fact, since also the viscosity and the diffusivity are pressure dependent, the effect of the pressure gradient on the unit efficiency deserves to be investigated. Furthermore, it is worth noting that, during the measurement of the solvent isotherms on Chiralcel-OD, a much lower adsorption kinetics has been observed compared to the other adsorbents investigated (cf. Chapter 3). Therefore a nonnegligible time might be required to establish the adsorption equilibria when the pressure level in a certain column of the unit is changed. This effect may be even more evident when modified carbon dioxide is used. Therefore, the occurrence of a transient period, where the fluid and adsorbed phase compositions change until the equilibrium is reached, may determine, in certain cases, a more complex behavior of the unit than the one represented in the frame of the equilibrium theory. Although all these phenomena deserve a deeper and more quantitative investigation in the future, the short-cut method de-
veloped here gives reliable design guidelines and predicts quite well the main features of the unit behavior as it is confirmed by the comparison with the experimental results. The experimental work (cf. Chapter 5) has been carried out in cooperation with NOVASEP (Nancy, F) on a pilot plant placed in their labs. The model system has been chosen so to represent the most important class of applications of small scale SMBs, i.e. enantioseparations. Furthermore, as it happens for the large majority of enantioseparations in SFC, the elution of the solute requires a modifier to be added to pure carbon dioxide. For the first time complete separation of a chiral compound has been carried out in a SF-SMB unit, operating both in ISO and PG mode. Furthermore, it is the first time that modified carbon dioxide has been used in a SF-SMB operating in PG mode. Although the very low selectivity, high purities in both outlet streams could be reached in both operating mode. However, in perfect agreement with the theory, the productivity in PG mode has been almost 3 times higher than in ISO mode. These first promising results should stimulate further investigation in the future, which must be mainly addressed to the process optimization as it is described in detail in section 5.5.

Chapter 6 of this dissertation is then devoted to the effect of pressure drop in a single chromatographic column. A method to derive reliable adsorption equilibria from chromatograms obtained in a column with non-negligible pressure drop has been presented. This approach has been applied to a model system for which linear chromatograms have been obtained and it has been shown that it is possible to extend it to overload chromatograms in order to get information about nonlinear adsorption equilibria. However, the discussion about column efficiency in the presence of a pressure gradient is more complex and further work is needed in this field.

We can therefore conclude that both the fundamental and applicative investigation carried out in this work has lead to new and interesting results that stimulate further work in the future. The fundamental approach presented here to address the adsorption thermodynamics of supercritical systems is not only of interest for chromatography, but will contribute to a deeper understanding of many other processes involving this phenomenon (catalytic processes, gas storage in natural or artificial reservoirs). The new theoretical tools and the experimental investigation has contributed to the development of SF-SMB technology. Until now, the high investment costs and the skepticism of the most traditional companies towards the use of high pressures, combined with a poor understanding of the
process have limited the development of this technology. However, in the last few years, several preparative batch SFC units have been installed, especially when the use and storage of large amounts of organic solvents is a critical issue. Furthermore, in this work it has been shown that SF-SMBs can be successfully applied also to enantioseparations exhibiting very low selectivity. Therefore, we believe that SF-SMB technique will attract in the near future the attention of the fine industry for separations of commercial interest.
### Chapter 8  

**Notation**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>surface area in Eq (2.1) [m$^2$]; empirical coefficient in Eq (3.1); van Deemter coefficient in Eq (6.11)</td>
</tr>
<tr>
<td>$a$</td>
<td>molecular size in Eq (2.15) [m]; empirical coefficient in Eq (4.3); empirical coefficient in Eq (6.3)</td>
</tr>
<tr>
<td>$B$</td>
<td>van Deemter coefficient in Eq (6.11)</td>
</tr>
<tr>
<td>$b$</td>
<td>Langmuir coefficient in Eq (2.12) and empirical exponent in Eq (1.1), Eq (4.11), Eq (5.1) and Eq (6.3)</td>
</tr>
<tr>
<td>$C$</td>
<td>B.E.T. coefficient in Eq (2.14); an Deemter coefficient in Eq (6.11)</td>
</tr>
<tr>
<td>$c$</td>
<td>fluid phase concentration [g/L]</td>
</tr>
<tr>
<td>$D$</td>
<td>pore diameter in Eq (3.1)</td>
</tr>
<tr>
<td>$D_{i2}$</td>
<td>diffusion coefficient of the solute in CO$_2$</td>
</tr>
<tr>
<td>$d_i$</td>
<td>empirical coefficient in Eq (4.12)</td>
</tr>
</tbody>
</table>
$F$ mass feed flowrate [g/min]

$f$ fugacity [bar]

$f_{i,j}$ net flux of species $i$ in section $j$ as defined by Eq (4.6)

$f_a$ fugacity of the adsorbed phase as it appears in Eq (2.14)

$G$ mass flowrate [g/min]

$\bar{G}$ average mass flowrate [g/min]

$H$ dimensionless Henry constant of component $i$

$H^*$ modified Henry constant as defined by Eq (4.14) [g/L]

$HETP$ height of theoretical plate [μm]

$\Delta H_0$ heat of sorption as it appears in Eq (2.13)

$\Delta H_\phi$ enthalpy change at constant surface potential as defined in Eq (2.20) [J/g]

$\Delta H^e_{m,int}$ integral molar enthalpy change at constant pressure as defined in Eq (2.22) [J/g]

$\Delta h^e_{sp}$ specific excess enthalpy change as defined in Eq (2.23) [J/g]

$\Delta H^e_{m,diff}$ differential enthalpy at constant amount adsorbed as defined in Eq (2.24) [J/g]

$k$ Boltzmann’s constant in Chapter 2 and capacity factor in Chapter 6

$K$ Langmuir equilibrium constant as defined in Eq (4.16) [L/g]

$K^*$ modified Langmuir equilibrium constant as defined in Eq (4.16) [g/g]

$L$ column length [cm]

$m$ flowrate ratio in section [g/L]

$M_{sp}$ overall inventory of stationary phase [g]

$m_0$ mass of the adsorbent plus the metal basket [g]

$m_A$ mass of the adsorbed CO$_2$ [g]

$m_{ads}$ mass of the adsorbent [g]

$m_{sinker}$ mass of the sinker [g]

$m^0_{sinker}$ mass of the sinker under vacuum [g]

$M_w$ molecular weight [g/mol]

$n$ adsorbed phase mass concentration [g/L]
Notation

$N$  saturation loading capacity [g/L]; number of plates in Eq (6.10)

$n$  adsorbed amount as defined in Eq (7) [g] and adsorbed phase concentration in Chapters 4 and 5 [g/L]

$n_m$  monolayer capacity [g/g]

$n_{abs}$  specific absolute adsorbed amount [g/g]

$n_{ex}$  specific excess adsorbed amount [g/g]

$P$  pressure [bar]

$PR$  productivity as given by Eq (4.36)

$Q$  volumetric flowrate [L/min]

$Q_s$  solid flowrate [L/min]

$R$  gas constant

$S$  column section [cm]

$S_{AB}$  selectivity, defined as $H_A/H_B$

$t$  time [min]

$t_0$  elution time of an unretained solute

$t_R$  retention time [min]

$t^*$  switch time [min]

$t_{eq}$  equilibration time [min]

$T$  temperature [K]

$u$  fluid superficial velocity

$u_s$  solid superficial velocity

$u_{sol}$  solute velocity in the chromatographic column as given by Eq (6.5)

$V$  column volume [L]

$V_0$  volume of the adsorbent plus the metal basket [L]

$V_A$  volume of the adsorbed CO$_2$ [L]

$V_{sinker}$  volume of the sinker [L]

$w$  fluid phase weight fraction; peak width in Eq (6.10)

$x_b$  fraction of sites occupied by fluid molecules in the bulk in Eqs (2.16) and (2.18)
146 Notation

coefficient in Eq (3.1); molar fraction in Eq (6.14)

compressibility factor

coordination numbers in Eq (2.18)

axial coordinate [cm]

Greek symbols

parameter in Eq (2.17) and given by Eq (2.18); geometrical parameter in Eq (6.1)

critical exponent in Eq (2.15); geometrical parameter in Eq (6.2)

geosmetrical parameter in Eq (6.2)

overall porosity

bed porosity

particle porosity

interaction energies in Eqs (2.17) and (2.18)

critical exponent in (2.15)

correlation length [m]

surface potential [J/g]

viscosity [Pa s]

bulk chemical potential as it appears in Eq (2.19)

chemical potential of fluid-fluid interactions as it appears in Eq (2.19)

chemical potential of fluid-solid interactions as it appears in Eq (2.19)

fluid phase density [g/L]

adsorbed phase density [g/L]

helium density [g/L]

parameter in Eq (2.16) and given by Eq (2.17)

balance signal under vacuum [g]

balance signal in helium atmosphere [g]

balance signal in CO₂ atmosphere [g]
Subscripts and superscripts

\( \text{F} \) feed

\( \text{H} \) high pressure in Eq (5.6)

\( \text{i} \) component index, \( i = A, B \)

\( \text{ISO} \) isocratic mode

\( \text{j} \) section index, \( j = 1, \ldots, 4 \)

\( \text{L} \) low pressure in Eq (5.6)

\( \text{m} \) modifier

\( \text{opt} \) quantity evaluated at the optimum

\( \text{PG} \) pressure gradient mode

\( \text{SMB} \) Simulated Moving Bed

\( \text{TMB} \) True Moving Bed

\( \text{0} \) reference value
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