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CONTROL OF FLOW RATE IN HIGH PRESSURE LIQUID CHROMATOGRAPHY

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SUMMARY

The various known principles for flow control in high pressure liquid chromatography are discussed from the point of view of applicability and reliability. A new, simple method for flow control is described. In this method, only a single unit is needed which serves as (1) pressure controller from 1 to 500 atm; (2) device for smoothing the pulsations of the pump; (3) safety valve; (4) pressure transducer from liquid to gas pressure; and (5) flow programmer. The new flow controller is not in the main flow stream of the liquid chromatographic apparatus but is connected in parallel with the separation column. No pressure is wasted for the control itself. The experimental and technical details of the instrument are described.

INTRODUCTION

For qualitative analysis in column chromatography, the flow rate of the mobile phase must be known at all times. In the case of concentration detectors (but not mass flow detectors), a knowledge of the flow rate is also necessary for quantitative analysis. The flow rate may be either constant or varied with time through the use of a well-defined programme. Good reproducibility of the flow rate is highly desirable, *e.g.* for peak identification.

For high pressure liquid chromatography, several instruments which fulfil these demands are known, which may be classified into those that use simple control of flow rate or pressure and those in which the flow rate (pressure) is automatically controlled. The expression "simple control" will be used in this paper when the flow rate (pressure) is regulated by an open control loop. These open control mechanisms measure neither the flow rate (pressure) nor deviations of it from a set value. Hence interference factors (*e.g.* malfunction of the pump) which may disturb the flow rate (pressure) cannot be balanced out. In contrast to this, an "automatically controlled" or closed loop circuit continuously measures the flow rate (pressure), and the measured value is fed back to the controller which changes the conditions automatically when deviations occur from a set value. Here interference factors do not affect the flow rate (pressure) or at least only slightly.

The advantages and disadvantages of open and closed loop controlled systems will not be discussed. However, the decision as to which system should be used will be influenced by the possible occurrence of interference factors. The methods developed to control the flow rate (pressure) in a liquid chromatograph will be discussed from this point of view, and a new, simple solution for an automatically controlled inlet pressure will then be described.

METHODS WITH SIMPLE CONTROL

Pressurized cylinders

A very simple method for flow-rate control is to place the eluent in a cylinder containing a piston which is moved either by a spindle drive or by gas pressure. With a synchronous motor acting on the spindle drive, the displaced volume per unit time is constant, resulting in a constant flow rate from the cylinder. When a constant gas pressure is used to move the piston, the liquid in the cylinder will be under the same pressure. Hence the column inlet pressure will also be kept constant. Both methods can be combined with a second smaller piston acting on the liquid. Then the final liquid pressure is a multiple of the pressure on the first, larger piston, the factor depending on the ratio of the areas of the two pistons. This principle is well known in hydraulic presses.

While the flow rate is controlled directly by the spindle drive, it is controlled only indirectly in the gas-pressurized cylinder. In the latter method, therefore, the flow resistance of the column should be constant. The column permeability may be affected in several ways, but it is a basic requirement in column chromatography that the permeability of the column is constant. When the permeability of the column changes, the packing and the height equivalent to a theoretical plate (HETP) of the column also change, and such a column should no longer be used. Consequently, control of the flow rate and the column inlet pressure (at constant outlet pressure) are equivalent. It should be noted that it is desirable to measure the flow rate and the inlet pressure at the same time.

The two methods of piston movement offer several advantages: (1) the experimental effort is small; (2) a flow free of pulsations is delivered, *i.e.* no damping mechanisms need be used; (3) the flow can be easily programmed if desired; and (4) the column flow rate depends only on the movement of the piston in the cylinder or the pressure on the piston. The action of both drive mechanisms on the flow rate is direct, and there are almost no interferences. Therefore, although it is only a simple process of control, the reliability that the column flow rate at a certain time has a certain value is quite good. At present, however, there seem to be great technical difficulties in tightening the piston sufficiently against the cylinder for long term reliability at pressures higher than about 100 atm. In addition, for the gas-pressurized piston, even a very small leakage will permit the gas to dissolve in the eluent. The pressure decreases downstream and the gas dissolved at high pressure escapes to form bubbles. These bubbles will then cause extreme noise in the detector, preventing the measurement of any meaningful signal. Finally, with the spindle-driven piston at high pressures, large mechanical forces occur which can be controlled only with difficulty. However, within their convenient pressure range, these methods are superior to others because of their simplicity.

High pressure pumps

To extend the range of pressure, high pressure pumps must be used. These pumps have been developed as dosing pumps against high pressures, and up to now they have not been modified for the special demands of high speed liquid chromatography. Because these pumps deliver an adjustable, constant amount of liquid per unit time, the flow rate in the column can be kept constant as well. The delivered flow, however, pulsates widely, and these pulsations must be smoothed by damping devices as already described[1]. Damping the pressure (or flow) pulsation of a liquid flow is analogous to the smoothing of an a.c. signal by a rectifier. For such a signal, the removal of the ripples of a full-wave rectification is much easier than that of a half-wave rectification. Consequently, a single pump should not be used to deliver the flow, but pumps with at least two heads 180° out of phase with one another.

With pressurized cylinders, the actual delivered flow rate is a direct function of the movement of the piston in the cylinder. On the other hand, high pressure pumps are either piston or diaphragm pumps or a combination of both. Thus their actual delivered flow rate is not a function solely of the movement of the piston or the diaphragm in the pump. The condition of the valves in the pump also determines the actual flow rate. The deposition of fine particles inside the valves may affect their functioning and thus alter the actual delivered flow rate. The influence of deposited particles on the functioning of the valves and the probability that fine particles occur in the eluent increase as the pressure increases. In this connection, it should be mentioned that especially when aqueous solvents are used, the pumped eluent must be filtered continuously to remove the products of mechanical erosion of the apparatus[2]. With regard to this interference of fine particles, it may be that the use of a dosing pump (which itself is an open control circuit) without it being followed by an automatic control unit may not be sufficient to yield a constant flow rate in all cases.

The natural wear of the valves also affects the flow rate, but this effect, however, occurs over time periods much longer than that for one analysis. The leakage loss of every valve increases with increasing pressure and consequently the delivered flow rate of these dosing pumps decreases at higher pressures. Considering the effects of both fine particles and natural wear of the valves, it is evident that when the flow rate of the pump is fixed at a certain value, the expected flow rate or column inlet pressure is not always attained. Hence the precise setting of the flow rate will be rather laborious because one has to measure the actual flow rate or column inlet pressure, readjust the pump, measure again *etc.*, until the correct value is obtained. As mentioned before, however, good reproducibility of a certain value of the flow rate is not absolutely necessary but only convenient. It should be noted that the pumps can continously deliver the flow, whilst a pressurized cylinder needs refilling and consequently the flow in the column must be interrupted. When refilling is necessary during an analysis, possibly when a peak is being eluted, and it is then difficult to detect quantitatively the compound involved. The retention times, however, may be only insignificantly affected with suitable construction of the cylinder, *i.e.* of sufficient capacity and with a short refilling time.

METHODS WITH AUTOMATIC CONTROL

In this case, the pump is not used as a dosing device but simply as a source of high liquid pressure which may vary within certain limits. Consequently, simple pumps can be used. One should remember again that the pumps in question are not constructed for the purpose intended here. Probably, in the future, manufacturers will construct simpler and cheaper pumps for high pressure liquid chromatography.

One possibility for the use of a closed loop control circuit with a controller for constant outlet pressure has been described[1] and will not be discussed here. In this paper, a new and simpler solution for the automatic control of the pressure is given. Whilst in the work of HÁLASZ *et al.*[1] three different units were needed for the functions of safety (upper pressure limit), controlling and smoothing, this is achieved here with one unit. Additionally, the same device acts as a pressure transducer from liquid to gas pressure and programmes the flow, if desired. The device is principally a controller for constant inlet pressure with a special diaphragm for smoothing the pulsations. This device and its particular functions are described in detail below.

DESCRIPTION OF THE CONTROLLER

Safety valve function

The principle of a constant inlet pressure controller is given in Fig. 1 schematic-

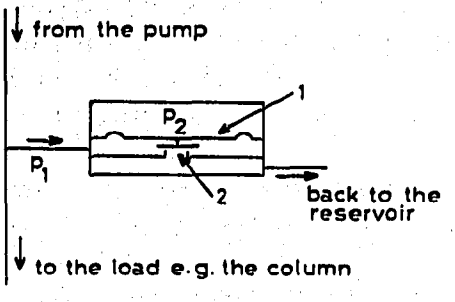

Fig. 1. Principle of an inlet pressure controller.

ally. If the pressure to be controlled, p_1, exceeds the set pressure, p_2, the diaphragm (1) rises and the excess liquid flows through the nozzle (2), causing p_1 to decrease (*vice versa* if $p_1 < p_2$). If the diaphragm should break, the apparatus is constructed so that p_1 and p_2 decrease by flow through the nozzle (2).

Damping of the pulsations

The device in Fig. 1 can limit the pressure only within certain upper and lower values, if that pressure pulsates. Therefore the capacity should be such that the apparatus accumulates and delivers flow, respectively, during the increasing and decreasing phases of one flow pulsation. This is possible when the controller shown schematically in Fig. 1 is constructed as shown in Fig. 2.

When $p_1 = 0$, the diaphragm (2) is forced into its resting position (lower full line of (2)) by the set gas pressure p_2 in the gas-tight dome volume above the diaphragm. When p_1 increases, the liquid flows through the inlet (1) into the controller

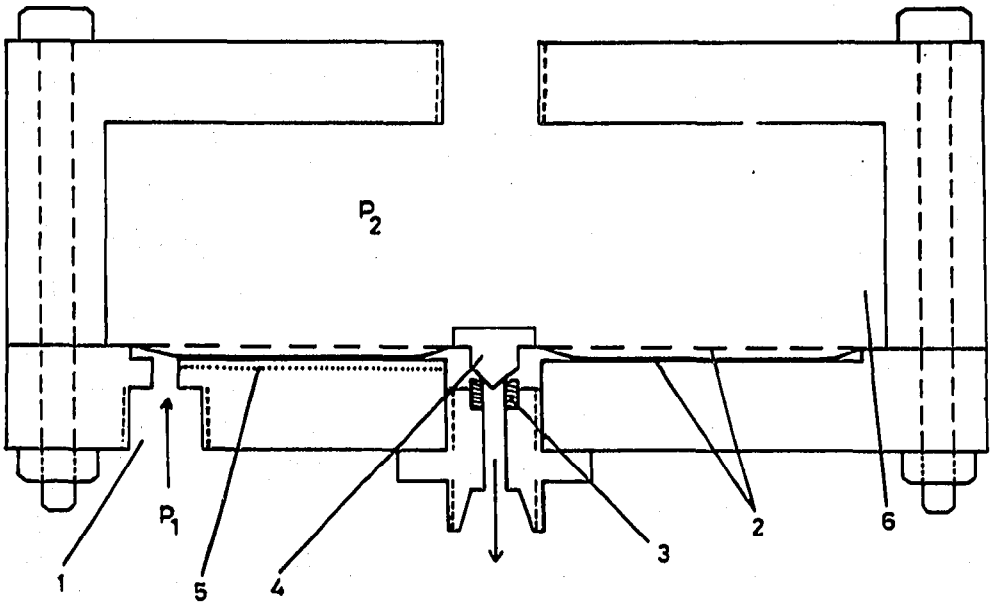

Fig. 2. Sectional view of the pressure controller (not in scale).

and lifts first the outer parts of the diaphragm as shown by the positions of the full and the dashed lines. By this process, the controller accumulates flow. Further increases in p_1 lift the diaphragm totally along with the tip (4) and the excess liquid flows through the nozzle (3) back into the reservoir. This occurs at the maximum of one pressure (or flow) pulsation. Decreasing p_1 in return cycle first causes the tip to close the nozzle. Then the outer parts of the diaphragm swing back into the resting position, and the flow is delivered by the controller. Hence the flow (*i.e.* the pressure p_1) is kept higher than that which the pump can deliver in the time period between two maxima of the flow (pressure) pulsations.

Of course, the "capacity" of the controller, *i.e.* the volume between the upper and the lower position of the diaphragm, must be larger, the greater the pulsations which the pump delivers are. With a triple pump with each head 120° out of phase with each other (Orlita K.G., Giessen, G.F.R., type M3 S4/4), a smoothing occurs of about $\pm$ 0.5% of p_1, independent of the pressure range. The "capacity" of the controller is about 0.5 cm^3. With a single pump, the controller fails to smooth the pulsations. The controller has not been tried with a twin pump with heads 180° out of phase with each other.

Pressure control

With the construction shown in Fig. 2, one can control liquid pressures from 1 atm up to the limit of the pump with a single unit. First the range 1–200 atm will be discussed, and later the extension of the control range above 200 atm. From Figs. 1 and 2, it is evident that p_1 can be controlled only within the range of the fixed counter-gas pressure p_2. Gas cylinders, however, are commonly pressurized to about 200 atm.

The lower limit of about 1 atm is determined by the elasticity of the stainless steel diaphragm. At pressures lower than 1 atm, the rigidity of the diaphragm material influences the movement of the diaphragm and hence the degree of control. The

control is 0.5% at every pressure, independent of the flow rate in the column as long as the flow does not exceed the capacity of the pump minus about 3 ml/min (the latter value is the flow rate that the controller itself requires, and this flow returns to the reservoir). The reproducibility of the column inlet pressure and hence of the flow rate depends only on the reproducibility of the (gas) manometer reading for the pressure p_2.

Pressure transducer

From the operation of the controller, it is evident that the liquid pressure p_1 is always kept in balance with the fixed gas pressure p_2. Consequently the controller acts as a pressure transducer from liquid to gas pressure. Accurate measurement of gas pressures, however, is much easier than that of liquid pressures. Additionally, in a liquid chromatographic apparatus, volumes through which the eluent does not flow must not be used. If such volumes exist, a change of eluent may lead to a very long drift of the detector signal, due to the fact that the former eluent flows from this volume only slowly by diffusion. Therefore Bourdon tube gauges should be used cautiously for measuring the liquid pressure directly.

OPERATION OF THE CONTROLLER IN THE LIQUID CHROMATOGRAPHIC APPARATUS

The chromatographic apparatus constructed is shown in Fig. 3 schematically. All materials in contact with the eluent are of stainless steel. The eluent flows from the pump through a small flow resistance (4), the filter and then through the injection port (1) into the controller and the separation column. The resistor (4) is only necessary for pressures above 200 atm. The filter is placed as close as possible to the column inlet. The pressure is controlled behind the filter, hence any pressure drop on it is unimportant. The controller is not in the main part of the apparatus but is connected in parallel with the column. Hence there is the same pressure at every point in the

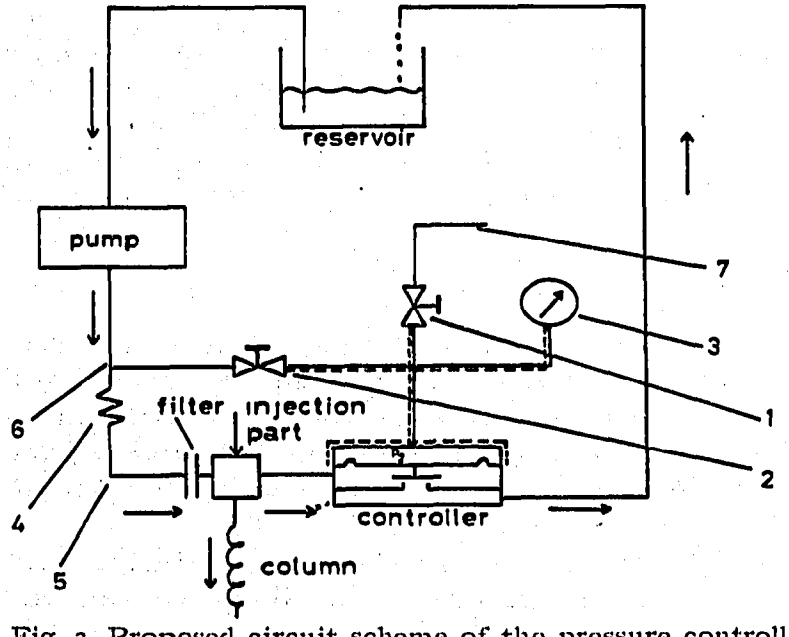

Fig. 3. Proposed circuit scheme of the pressure controller.

apparatus (neglecting the small pressure drop at the resistor (4)) and no pressure is wasted for the purpose of control.

Pressures up to 200 atm

The line (7) (Fig. 3) is directly connected to a high pressure gas cylinder (not shown). While valve (2) is closed, the dome of the controller is filled with gas via the valve (1). The increasing (gas) pressure p_2 is observed on the manometer (3). At the desired fixed pressure, valve (1) is closed. Because some heat of compression is generated by this process, p_2 decreases by about 1–3% when valve (1) is closed, and when the pump is switched on, p_2 increases by about 1% due to the lifting of the diaphragm in the controller out of its resting position which decreases the volume of the dome.

The dome of the controller and the other volumes filled with pressurized gas (dashed lines in Fig. 3) are gas-tight and p_2 therefore need not be controlled. However, the pressure of a gas in a closed volume varies with temperature by about 0.3%/°C in the temperature range of interest, and if variations in the room temperature of more than 2° are expected, one should place the dome of the controller in a thermostated water bath. Valve (1) should be used for filling and venting the dome, since the use of an additional valve for venting increases the chance of leakage. At column inlet pressures up to 200 atm, the resistor (4) and the valve (2) are not necessary and can be omitted.

Pressures greater than 200 atm

With the operation described above, the pressure range is limited to 200 atm. After filling the dome with gas, however, the gas can be compressed further by the pump itself. At the position marked (5) (Fig. 3), the liquid pressure is equal to the gas pressure p_2 (assuming that the pressure drop at the filter is negligible). Due to the flow resistance (4) and the pressure drop across it, the liquid pressure at the position marked (6) is somewhat higher, about 5–10 atm. When the valve (2) is opened, the liquid then streams into the dome because the (gas) pressure is 5–10 atm lower than at position (6). By this process, the gas is more compressed, p_2 increases and hence the liquid pressure at positions (5) and (6) also rises. With a dome volume of about 50 cm^3, p_2 can be increased by a factor of three by forcing liquid into the dome. Further compression causes the controller to fail in its smoothing function. Obviously the total compressibility of the gas–liquid mixture in the dome becomes so poor that the diaphragm can no longer swing elastically.

For clarity in Fig. 3, the controller is drawn in the same position as in Figs. 1 and 2, but when pressures above 200 atm are used, the controller must be mounted upside down. In this case, the liquid is forced out of the dome when the pressure is lowered by venting the dome via valve (1).

Flow programming

Up to 200 atm, the gas pressure p_2 can be programmed by methods already described[3]. The liquid pressure can therefore also be programmed and hence the flow rate in the column.

At pressures above 200 atm, the operation described in the previous subsection may be applied to obtain a pressure programme. As long as valve (2) is open

the pressure in the dome (p_2) and the liquid pressure increase. The rate of the pressure increase depends on the flow resistance of valve (2) and the dome volume. The reproducibility of this simple pressure programme is determined by the reproducibility of the delivery rate of the pump, however. The same objections must be raised here as those already discussed for high pressure pumps. If flow programming in high speed liquid chromatography in the future seems advantageous, however, it is not difficult to use a second controller to keep the flow in the dome volume constant.

EXPERIMENTAL DETAILS

The diaphragm of the controller consists of a 0.1-mm stainless steel sheet which is well supported so that high pressures in the dome cannot rupture it. It is therefore not necessary to vent the dome after a run, and hence the consumption of gas is low and small gas cylinders can be used. The controller itself is made entirely out of stainless steel.

The gas tightness of the dome and the other volumes filled with gas (dashed lines in Fig. 3) is important because it determines the constancy of p_2 and hence of

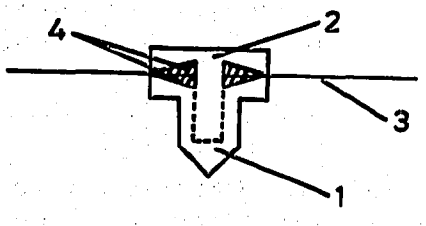

Fig. 4. Fixing and tightening of the tip at the diaphragm.

the liquid pressure. The lower and upper parts (dome) of the controller are kept together by bolts and the diaphragm is sealed in the middle using Teflon tape. The tip is fixed at the diaphragm as shown in Fig. 4. The internally threaded tip (1) and the bolt (2) are conical in shape. Teflon tape is pressed into the resulting space (4) (hatched parts) between the bolt and the diaphragm (3) on one side and the tip and the diaphragm on the other side. When the bolt and tip are tightened, the Teflon flows into all the spaces so that the system is sealed completely gas-tight.

The valves (1) and (2) (Fig. 3) are machined out of stainless steel*. Although these valves have no soft seat, they close gas-tight against pressures of several hundred atmospheres. To achieve this easily, molybdenum sulphide-based lubricant should be put on their stem and seat. Normal leakage rates of the (gas) pressure p_2 are 0.5–1 atm/day at a level of 100 atm.

The seat in the nozzle (3) (Fig. 2) of the controller (hatched parts) is made of a hard polyamide. The nozzle itself is a modified stainless steel Ermeto fitting. The distance between tip (4) and seat (3) is important for the correct working of the controller. If this distance is too small, the diaphragm cannot swing unhindered, and the smoothing effect is poor. On the other hand, if this distance is too large, the controller works at high pressures only when the tip is forced into the seat. At lower

* Whitey Research Tool Co., Emeryville, Calif., U.S.A., type 31RS4.

pressures, slow oscillations around the fixed pressure occur. If the tip cannot close the nozzle at all because this distance is too great, the liquid pressure does not increase. A small channel (5) (Fig. 2, dotted line) milled into the support of the diaphragm ensures that the liquid flows unrestricted under the diaphragm from the inlet (1) to the nozzle (3).

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