

# Reduction in large-scale adsorption chromatography unit costs by use of 30-Å Sorbsil C30 silica

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(First received November 22nd, 1991; revised manuscript received January 31st, 1992)

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## ABSTRACT

Adsorption chromatography is being increasingly used to purify products on an industrial scale. A major cost factor is the purchase, recycling and disposal of the large volumes of solvents used in the process. Silicas of higher loading capacity are required to reduce the solvent costs and we have shown that specifically designed silicas with a pore size of 30 Å can provide the capacity increase. Although historically it has been believed that silica of pore size less than 60 Å cannot perform satisfactorily, it is shown that Sorbsil C30 gives good kinetic performance ( $h < 2$ ), and that the significantly higher surface area per unit column volume leads to much higher loading capacities. Data from small-scale breakthrough curves for laboratory- and pilot-scale elution chromatography show increases in capacity between 50 and 250% compared with conventional 60-Å silicas. Data models for large-scale operations show a significant reduction in processing costs from the use of Sorbsil C30, owing to decreased solvent consumption and a smaller sample recovery plant with the additional benefit of reduced contamination of the sample by solvent impurities.

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## INTRODUCTION

Interest in and the use of process-scale chromatography have been growing steadily as the regulatory demands on product purity exceed the ability of conventional process purification steps to meet those demands. Although reversed-phase process chromatography has been on the increase [1], by far the largest utilization on the process scale is adsorption chromatography using silica. Over the last few years, interest has focused on the use of smaller particle silicas with an average size range of 10–20 μm [2]. These smaller particles give higher efficiency, leading to better separation of complex mixtures. For simpler mixtures, the higher efficiency can be put to good effect by increasing the solvent strength

to reduce capacity factors and save on solvent consumption.

The use of small-particle media, particularly in the 10-μm range, is not without problems as media, equipment and maintenance costs are high. Although in some instances these costs can be justified, many processes run with larger particles and cannot at this stage in their life justify the capital investment required for their change. One area which has received little attention is the improvement in the loading capacity of the media. Such improvements can benefit users of materials of all particle sizes and can be implemented at no capital cost as no modifications are required to the chromatographic plant to achieve a higher throughput. A higher surface area, provided that it is accessible to the solute, would allow a potentially higher loading capacity as deviation from the linear part of the adsorption isotherm occurs at a particular surface

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concentration for a given phase system. One way of achieving a higher surface area is to use a silica of small pore size as surface area tends to increase as the pore size is decreased. Historically, 60-Å, 500 m<sup>2</sup> g<sup>-1</sup> silicas have become the standard for high-capacity adsorption chromatography. The use of media of smaller pore size has been discouraged by the assertion that “micropores” cause slow diffusion kinetics and hence poor efficiency [3,4]. Although this may occur with some media, the use of a specifically designed particle with a mean size of 30 Å and a minimum of pores in the <20 Å range can give a high surface area with excellent mass transfer kinetics. This paper discusses the development, properties and application of a novel silica of high surface area and small pore size that shows significant loading advantages over conventional 60 Å silica, giving a higher throughput and substantial solvent savings.

## EXPERIMENTAL

### Materials

The materials used were obtained from the following sources: Sorbsil C30 and C60, 15–20, 20–40 and 40–60 μm, Crosfield Chromatography (Warrington, UK); Kieselgel 60, 40–60 μm (9385), E. Merck (Poole, UK); Spherisorb X and W, 10 μm, Phase Separations (Queensferry, UK); Pro 10 and Zorbax, 10 μm, DuPont (Warrington, UK); Matrex 60A, 10 μm, Amicon (Stonehouse, UK); Partisil, 10 μm, Whatman (Maidstone, UK); hexane, Rathburn (Walkerburn, UK); heptane, ethyl acetate, 2-propanol and tetrahydrofuran, Rhône Poulenc Laboratory and Products (Manchester, UK); and Agrochemical Exploratory Herbicide (Mw 400), ICI Agrochemicals (Jealott's Hill, UK).

### Equipment

The chromatographic system consisted of a Pye Unicam PU 4010 pump, Pye Unicam PU 4020 UV detector, Rheodyne Model 7125 injection valve and Hewlett-Packard HP 3393A reporting integrator.

Large-scale chromatography was carried out on a Prochrom 150 preparative liquid chromatograph with a 15 cm I.D. axially compressed column.

### Procedure

Stainless steel columns (12.5 cm × 0.46 cm I.D.

for Sorbsil C30 and 12.5 cm × 0.50 cm I.D. for Kieselgel 60) were dry packed with the 40–60-μm silica (1.32 g per column). Media of smaller particle size were slurry packed into 25 × 0.46 cm I.D. columns.

Samples of phthalate esters were prepared as either 10% (w/w) solutions in the relevant mobile phase or as neat mixtures of 50% (w/w).

Columns were purged with 2-propanol (20 column volumes) prior to purging with eluent (30 column volumes). The eluent was 2-propanol in heptane, adjusted in flow-rate to give equal linear velocities (1.8 ml min<sup>-1</sup> for Sorbsil C30, 2.2 ml min<sup>-1</sup> for Kieselgel) and in composition to give similar capacity factors for the dimethyl phthalate peak (e.g., 3% 2-propanol for C30 and 1% propanol for Si 60). Size-exclusion chromatography was carried out at 1 ml min<sup>-1</sup> with tetrahydrofuran (THF) using 0.25% w/v solutions of polystyrene standards.

The breakthrough curves of methanol in ethyl acetate were obtained by purging the columns with twelve column volumes of ethyl acetate. The column was then disconnected and the system purged with 1% methanol in ethyl acetate. The column was re-connected and purged with 1% methanol in ethyl acetate at 1 ml min<sup>-1</sup>. The retention volume to 50% breakthrough corrected for the column void volume was recorded.

The capacity factor of an experimental herbicide was measured for a range of silicas using 25% ethyl acetate in hexane. The breakthrough curves were measured for this compound on these silicas in an analogous manner to that described above.

Large-scale chromatography was carried out on a Prochrom 150 system using a 15 cm I.D. column. A 5-kg amount of 20–40-μm packing was axially compressed and eluted with hexane–ethyl acetate (75:25) at 2 l min<sup>-1</sup>. Increasing amounts of herbicide were injected and the major component (ca. 85%) was collected and assayed. The loading capacity was defined when the purity just dropped below 98%.

## RESULTS AND DISCUSSION

### Physical properties of Sorbsil C30

The standard BET-derived pore diameter plots (Fig. 1) show the narrow pore-size distribution of the Sorbsil C30 gel with a notable reduction in

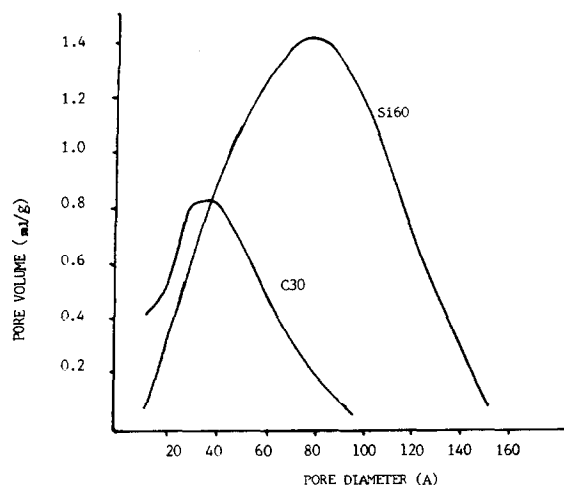


Fig. 1. Nitrogen adsorption pore volume plots for Sorbsil C30 and Merck Si 60.

pores of  $<25 \text{ \AA}$ . This lack of small pores in the  $10\text{--}20 \text{ \AA}$  range contributes to excellent kinetics, as is shown by the Van Deemter plot obtained for Sorbsil C30 ( $15\text{--}20 \mu\text{m}$ ). This shows (Fig. 2) an optimum

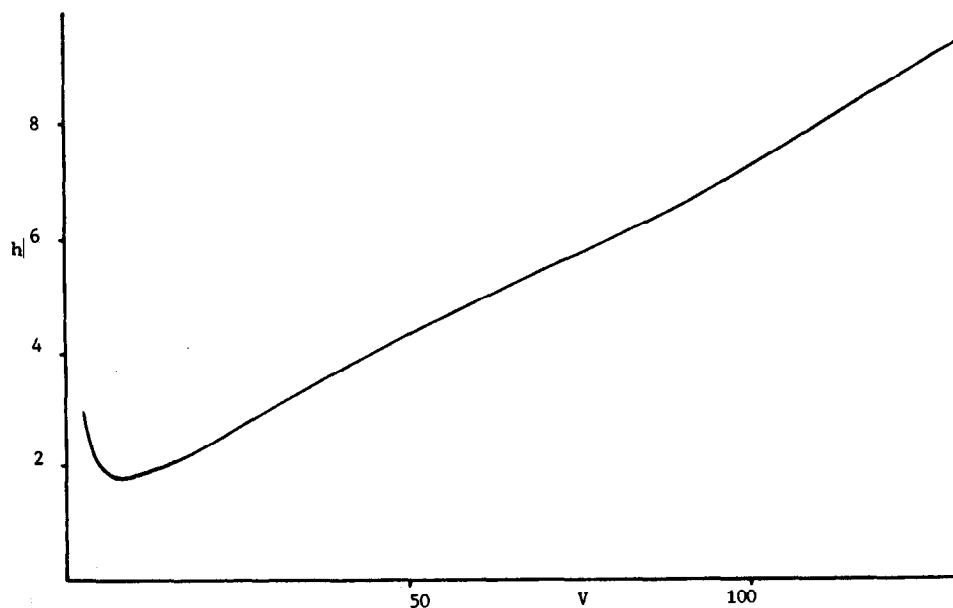


Fig. 2. Plot of reduced plate height versus reduced velocity for Sorbsil C30 ( $15\text{--}20 \mu\text{m}$ ). Column,  $12.5 \times 0.46 \text{ cm}$  I.D.; eluent, methanol–heptane (1:99); solute, nitrobenzene.

reduced plate height of 1.7 and a low  $C$  term (0.07).

Size-exclusion curves (Fig. 3) show that both the 30- and 60- $\text{\AA}$  gels exhibit exclusion behaviour from MW 200 upwards. The curves start to show significant divergence in the MW range 700–1000 and this marks the molecular weight range where the potential loading capacity advantage of the high-surface-area 30- $\text{\AA}$  gel would be expected to diminish.

The low pore volume ( $0.6 \text{ g ml}^{-1}$ ) of Sorbsil C30 together with the optimized processing route gives a gel of very high mechanical strength. Using the equations developed by Meissner [5], the crush strength is estimated to be 28 000 p.s.i. The Sorbsil C30 gel has been re-used extensively in a Prochrom system without noticeable mechanical attrition. Sorbsil C silicas are manufactured using deionized water and show a significant improvement in impurity levels compared with technical-grade silicas (Fig. 4).

#### Overload performance

Loading capacity in adsorption chromatography is, to a first approximation, proportional to accessible surface area per unit column volume. Table I

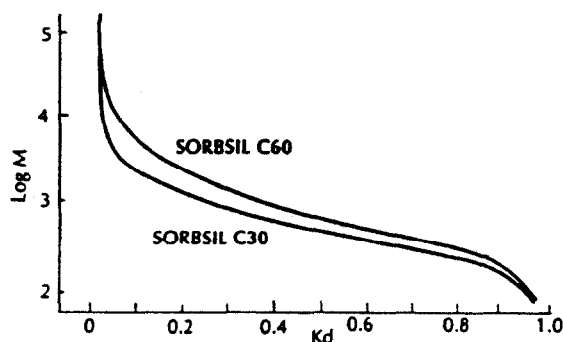


Fig. 3. Size-exclusion curves for linear polystyrene in THF on Sorbsil C30 and C60.  $K_d$  = Fraction of pore volume accessible.

gives typical values for various silicas taken from manufacturers' literature.

Breakthrough curves of 1% methanol in the ethyl acetate (Fig. 5) which give a measure of relative loading capacity gave a good correlation with relative surface areas (Table II).

The extension of this study to solutes of higher molecular weight will be reported subsequently, but initial data show that the capacity advantage of

Sorbsil C30 is maintained up to at least MW 500. The study was extended to a wider range of silica supports and the saturation capacity of an exploratory herbicide was measured by the breakthrough technique. In Fig. 6, the saturation capacity is plotted against the capacity factor of the herbicide on the same column. This gives a remarkably linear plot and indicates the usefulness of simple capacity factor measurements in predicting relative loading capacities. Further work is required to establish the generality of this result, but if confirmed it provides a means of rapid product screening for maximum loading capacity.

In order to study overload effects of the 30-Å *versus* conventional media in the elution mode, the solvent composition had to be adjusted to give similar  $k'$  values on columns of different retentivity for the most retained compound. As Sorbsil C30 is more retentive owing to the high surface area, a stronger solvent is required than for conventional 60-Å media (*e.g.*, 3% vs. 1% 2-propanol). This provides an additional benefit in large-scale use as the stronger solvent aids sample solubility, reducing the sample volume for low-solubility samples.

The loading capacity under elution conditions

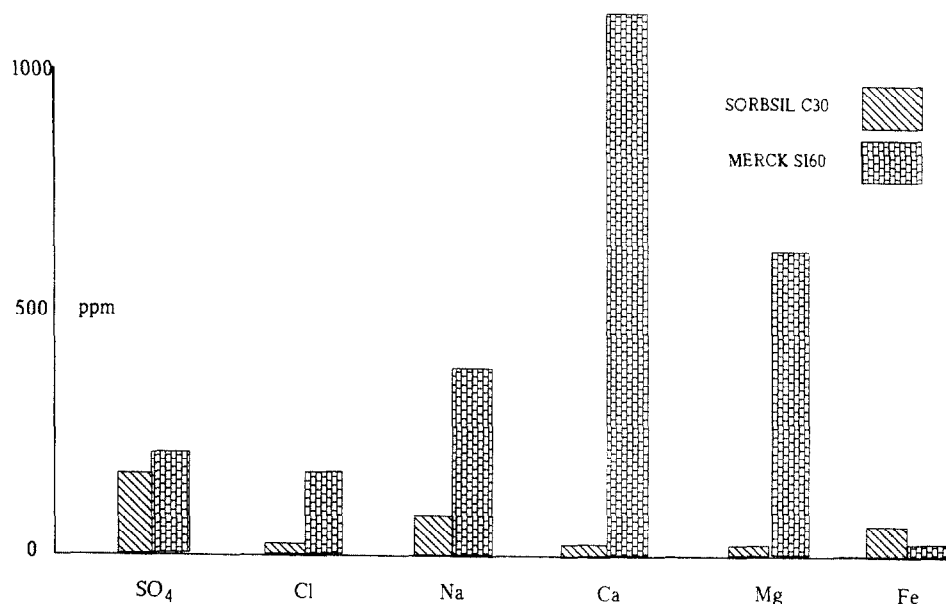


Fig. 4. Impurity profiles (ppm) for Sorbsil C30 and Merck Si 60.

TABLE I  
PROPERTIES OF DIFFERENT SILICAS

Packing	Surface area (m <sup>2</sup> g <sup>-1</sup> )	Packing density (g ml <sup>-1</sup> )	Surface area (m <sup>2</sup> ml <sup>-1</sup> )
Spherical 120 Å	220	0.62	130
Spherical 100 Å	340	0.50	170
Irregular 60 Å	500	0.55	275
Irregular 60 Å	540	0.55	297
Sorbsil C60	550	0.55	303
Sorbsil C30	700	0.63	441

was established for two solvent strengths by chromatographing a 50:50 (w/w) mixture of dibutyl and dimethyl phthalates up to 16 mg of each ester per ml of column volume (25 mg g<sup>-1</sup> of packing) (Figs. 7 and 8). Although of similar structure, the two esters show different adsorption isotherms. The butyl ester shows Langmuir-type adsorption with decreasing retention and peak tailing on overload whereas the dimethyl ester shows anti-Langmuir adsorption with increasing retention time and peak fronting. Visual inspection indicates that approximately twice the amount of ester is required to give a similar degree of peak tailing/fronting on the Sorbsil C30. Plots of retention time against mass injected (Figs. 9 and 10) show a much greater resistance to overload for the 30-Å material and similar results were obtained using the weaker solvent system. The change in capacity factor on a range of overload criteria, 10%, 25% or 50%, shows the 30-Å material to be less sensitive to overload by factors between 2 and 5.

TABLE II  
CAPACITIES AND SURFACE AREAS OF 60- AND 30-Å SILICAS

Packing	Methanol adsorbed per ml of column (mg)	Measured relative capacity	Relative surface area per ml (%)
Merck Si 60	120	91	91
Sorbsil C60	132	100	100
Sorbsil C30	197	149	146

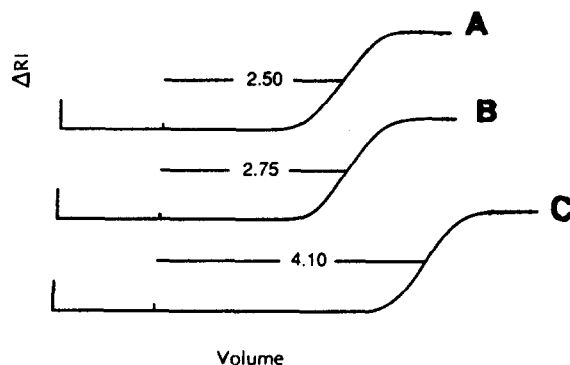


Fig. 5. Breakthrough curves on methanol–ethyl acetate (1:99) on (A) Merck Si 60, (B) Sorbsil C60 and (C) Sorbsil C30.

Most theoretical models have assumed that the critical pair(s) of compounds have similar-shaped adsorption isotherms [6–8]. However, our findings, which are by no means unique, illustrate the need to determine the isotherm shape for each application. This observation goes some way to explaining the range of increased loading capacities found in practice. These range from 0 to 300%, although the nominal increase in surface area per ml of Sorbsil C30 over Merck Si 60 is 60%. Part of this discrepancy is probably due to the difference in the shapes of the adsorption isotherms. In the phthalate ester case, the peaks move apart as they overload and the overloading of the lower capacity phase is partially compensated for by this peak shift. For the other extreme, where the first peak moves back and the second peak moves forward, resolution will be lost on the lower capacity phase at a much reduced sample loading. An understanding of this phenomenon is crucial in selecting the most appropriate phase system for a preparative separation and will be the basis for future experimentation.

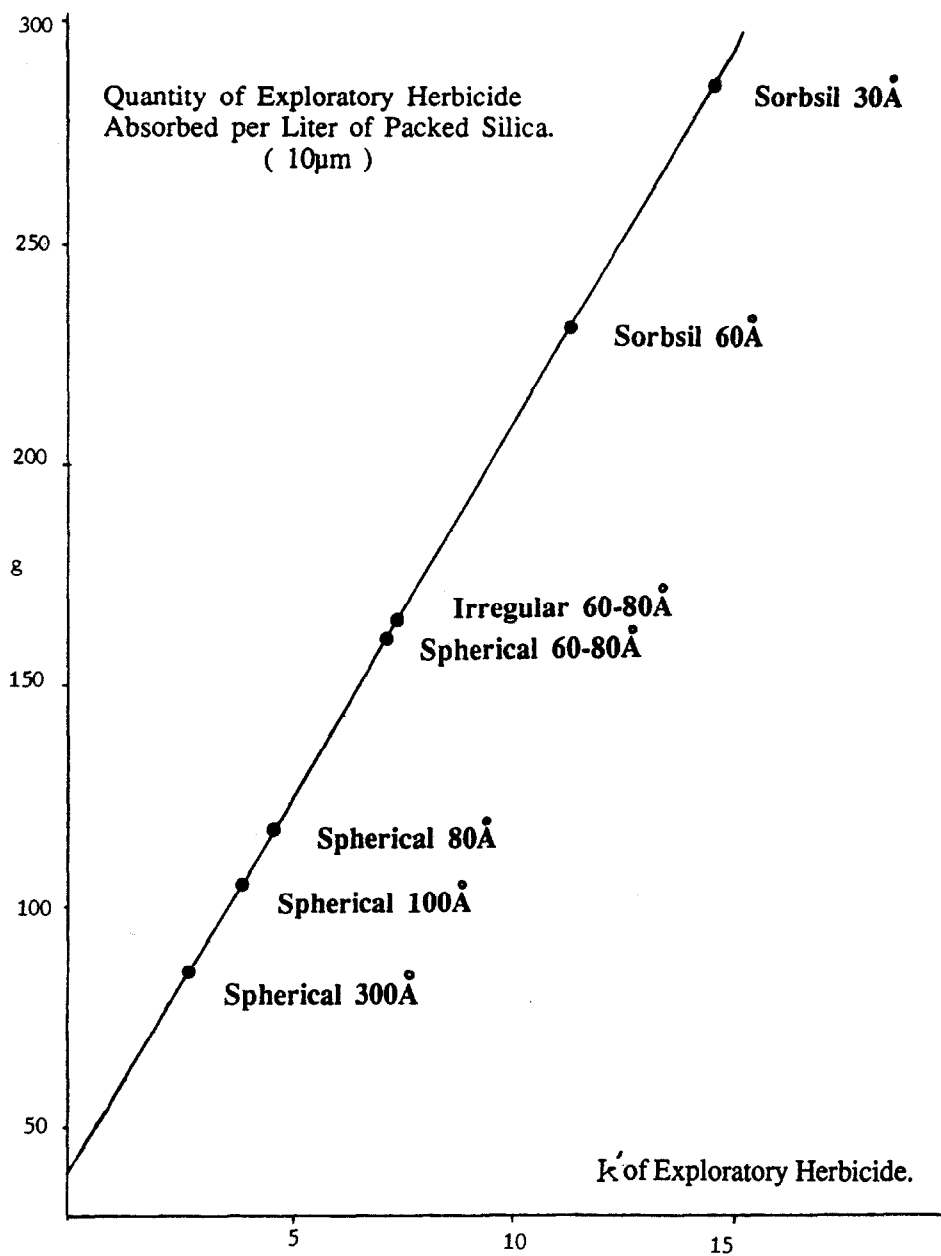


Fig. 6. Plot of amount of exploratory herbicide adsorbed per unit column volume against capacity factor of herbicide.

For a 64-mg injection, the dimethyl phthalate peak was collected and subsequently analysed by high-performance liquid chromatography. The results are given in Table III, and clearly show that

the Sorbsil C30 provides higher purity, lower solvent consumption and higher fraction concentration, all of which, as will be discussed, provide substantial cost reduction benefits in large-scale chro-

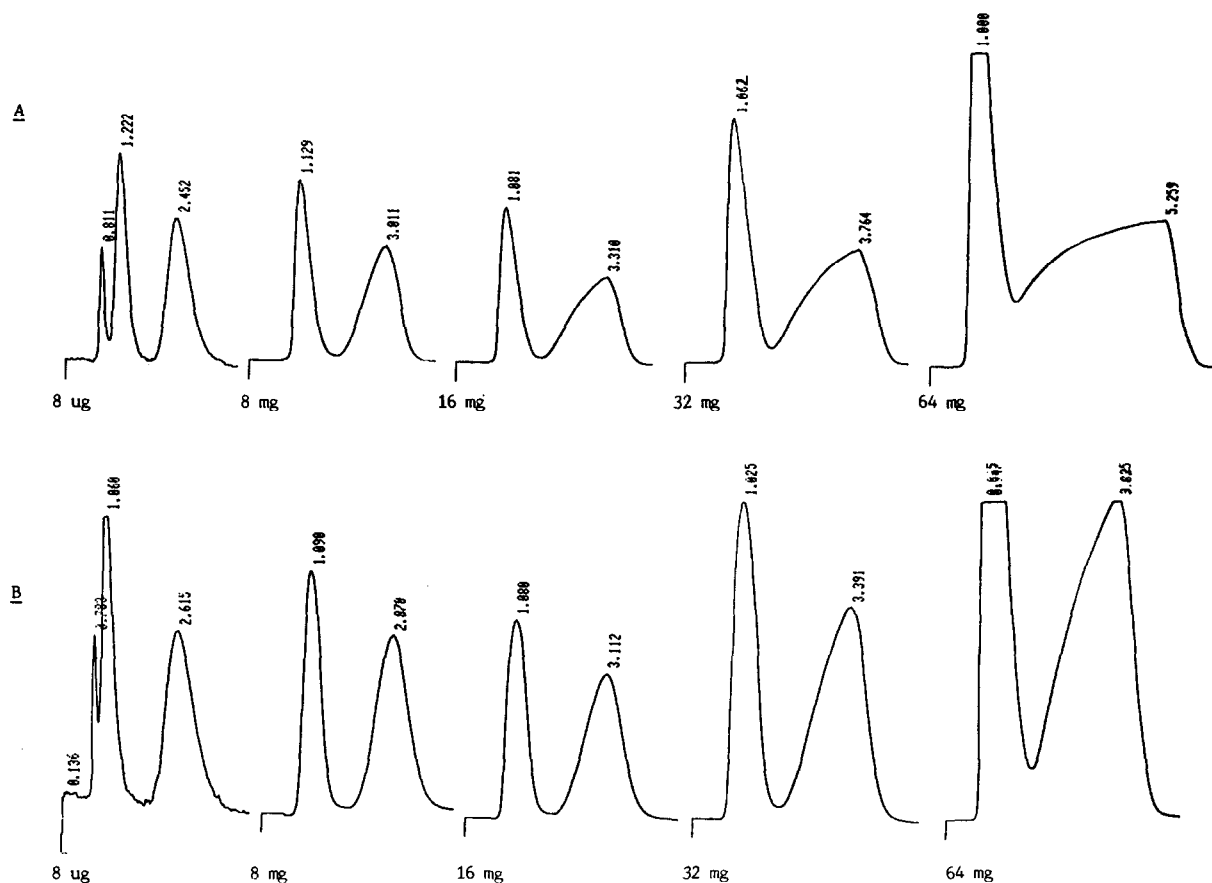


Fig. 7. Separation of 8  $\mu\text{g}$ , 8 mg, 16 mg, 32 mg and 64 mg of phthalate esters on (A) Merck Si 60 and (B) Sorbsil C30 (40–60  $\mu\text{m}$ ). Solvent: heptane–2-propanol, 1:99 for Si 60 and 3:97 for Sorbsil C30. Numbers at peaks indicate retention times in min.

matography. If a smaller mass of 32 mg were to be used on the Si 60 column, the purity would increase but the throughput would halve, the solvent consumption per unit throughput would double and the fraction volume would double.

#### Large-scale evaluation

Sorbsil C30 (20–40  $\mu\text{m}$ ) was compared with a conventional silica of high surface area (Matrex 60  $\text{\AA}$ ) in a Prochrom 150 system for the purification of an exploratory herbicide. The purity of the starting material was 85% (Fig. 11) and a minimum of 98.7% final product purity was required. The sample mass injected on to the 60- $\text{\AA}$  column was increased as the purity of the collected material was determined.

The results show that up to 200 g could be loaded on to the column before the purity fell to below 98.7% (Table IV), Figs. 12 and 13). The recovery at this load was 82%.

A similar-sized column of Sorbsil C30 (20–40  $\mu\text{m}$ ) required a slightly stronger solvent to give equivalent performance in terms of efficiency, capacity factor, selectivity and back-pressure, but allowed a sample load of 520 g and a recovery of 79%, which gave a purity of 98.8% (Figs. 14 and 15). This gives a 250% increase in product throughput with the potential for substantial cost savings.

Subsequent studies with smaller particle Sorbsil C30 15–20  $\mu\text{m}$  showed that at lower loadings, relatively high plate counts can be achieved in the Prochrom system 18 000 plates  $\text{m}^{-1}$ ,  $h = 3$ ) (Fig. 16).

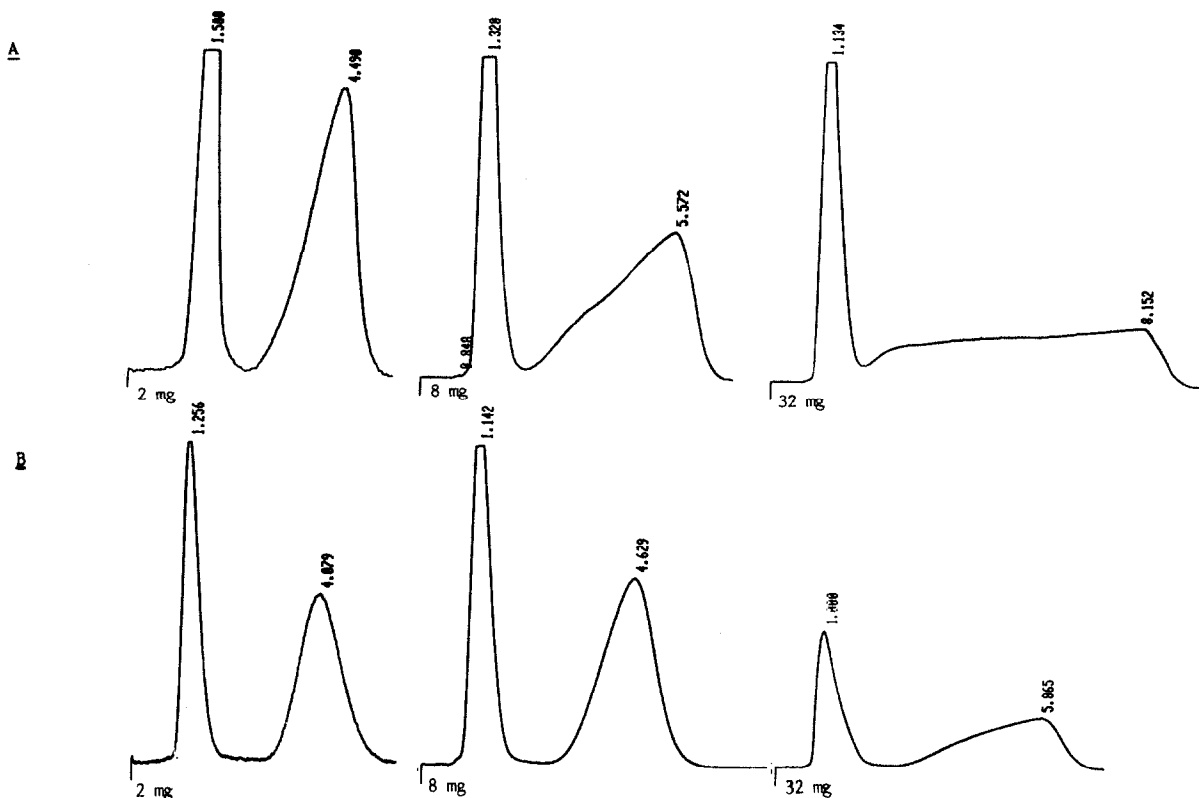


Fig. 8. Separation of 2, 8 and 32 mg of phthalate esters on (A) Merck Si 60 and (B) Sorbsil C30 (40–60  $\mu\text{m}$ ). Eluent: 2-propanol–heptane, 0.5:99.5 for Si 60 and 1:99 for Sorbsil C30. Numbers at peaks indicate retention times in min.

In some preparative systems (CEDI, 25  $\times$  10 cm I.D.) plate heights of less than 1.5 (40 000 plates  $\text{m}^{-1}$ ) have been achieved (Fig. 17) with Sorbsil C60 (15–20  $\mu\text{m}$ ).

#### Process economics of elution chromatography

Media of high loading capacity will provide cost savings from two main sources: solvents and plant.

*Solvent savings.* For a given throughput, less Sorbsil C30 will be required. The exact reduction will depend on the actual increase in capacity. This reduced volume of silica will require a similarly reduced volume of solvent for unit throughput. The solvent requirement is also reduced by the slightly lower relative column void volume of Sorbsil C30 (0.72 ml of solvent per ml of empty column) compared with 60- $\text{\AA}$  media (0.76).

Numerically, the cost saving per annum ( $S$ ) on solvents is given by the equation

$$S = a b c d [f - g / (1 + e)]$$

where  $a$  = mass of 60- $\text{\AA}$  silica used per annum;  $b$  = number of column volumes of solvent used per run;  $c$  = cost of solvent per litre (purchase, recycle, disposal);  $d$  = number of cycles before media replacement;  $e$  = fractional increase in loading capacity; and  $f$  and  $g$  = respective solvent volume in 1 g of packing. For a 60- $\text{\AA}$  packing with relative void volume 0.76 and a packing density of 0.55  $\text{g ml}^{-1}$   $f$  is 0.76/0.55 = 1.38 and for Sorbsil C30 the value of  $g$  is 0.72/0.63 = 1.14.

Three worked examples are given in the Appendix and demonstrate significant savings (45%) in



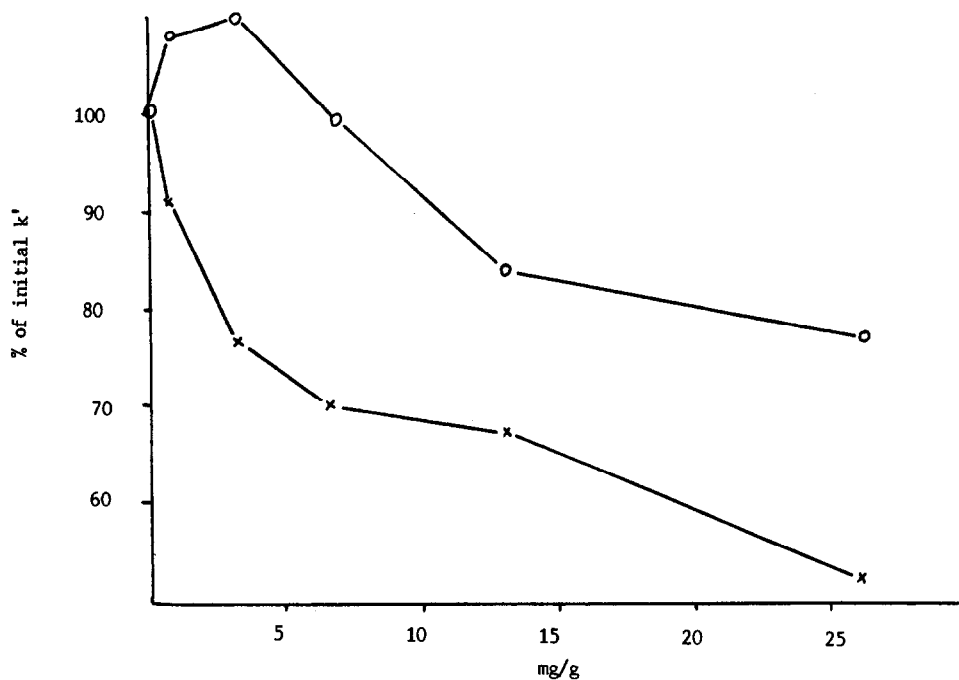


Fig. 9. Percentage change in capacity factor for dibutyl phthalate as a function of load ( $\text{mg g}^{-1}$ ) for (x) Merck Si 60 and (o) Sorbsil C30. Eluent: 2-propanol-heptane (1:99).

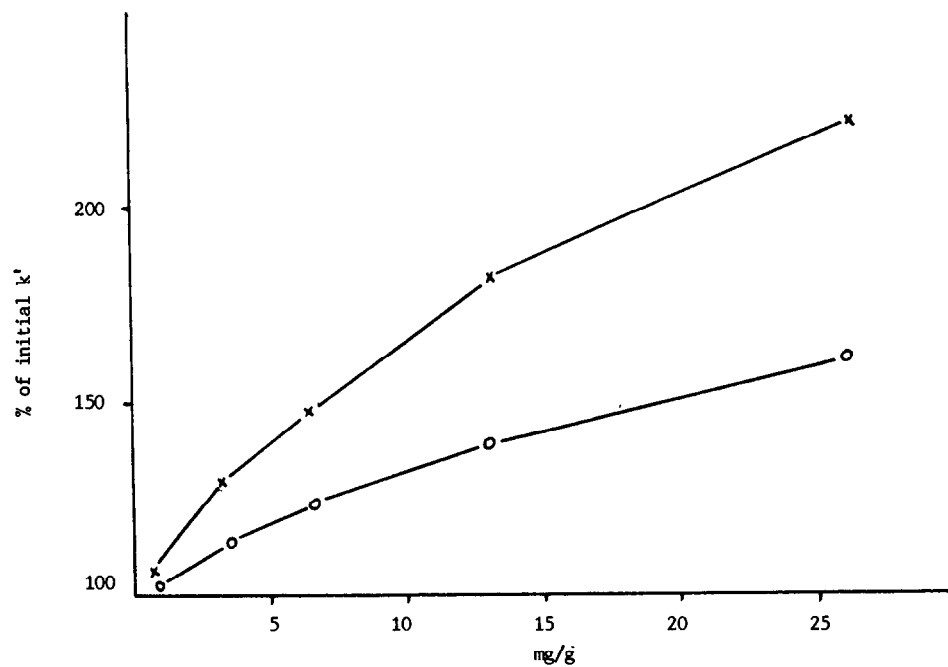


Fig. 10. Percentage change in capacity factor for dimethyl phthalate as a function of load ( $\text{mg g}^{-1}$ ) for (x) Merck Si 60 and (o) Sorbsil C30. Eluent: 2-propanol-heptane (1:99).

TABLE III  
PARAMETERS OF DIMETHYL PHTHALATE PEAKS  
FROM 64-mg INJECTION

Parameter	Si 60	Sorbsil C30
Peak volume (ml)	10.1	5.8
Mass recovered (mg)	32.8	33.8
Recovery (%)	98.5	101
Purity (%)	97.3	99.1
Concentration (mg ml <sup>-1</sup> )	3.24	5.86
Total solvent consumption per run (ml)	14.3	9.18

TABLE IV  
PURITY VS. MASS INJECTED FOR HERBICIDE ON MA-  
TREX 60 Å (20-40 μm) IN PROCHROM COLUMN

Sample load (g)	Product purity (%)
100	99.99
150	99.91
200	98.99
250	98.63

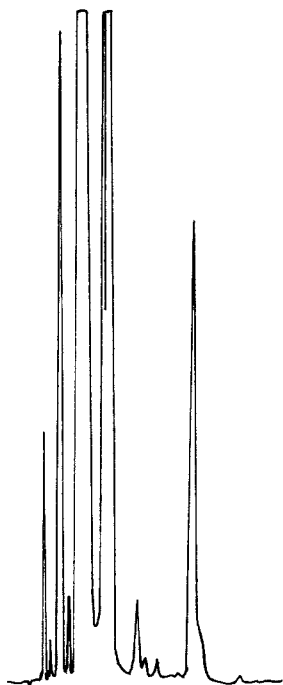


Fig. 11. Analysis of starting exploratory herbicide.

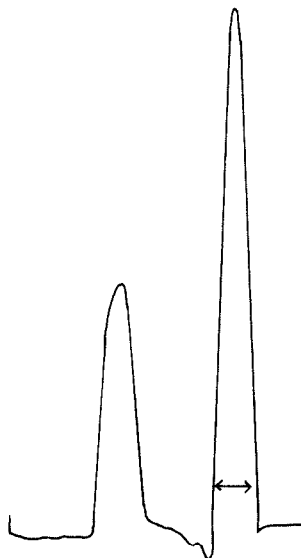


Fig. 12. Separation of 200 g of herbicide on a 68 × 15 cm I.D. column of Matrex 60 Å (20-40 μm). Eluent, ethyl acetate-hexane (20:80) at 2300 ml min<sup>-1</sup>; backpressure, 23 bar; chart speed, 300 mm h<sup>-1</sup>; injection volume, 2.5 l. Product fraction collected between arrows. Throughput 0.6 kg/h.

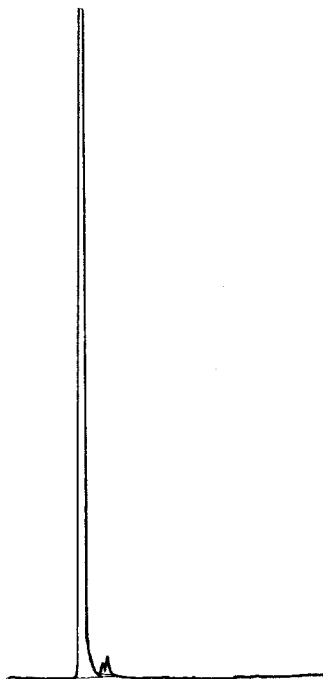


Fig. 13. Analysis of product fraction collected between arrows in Fig. 12 from application of 200 g of herbicide on a Matrex 60 Å (20-40 μm) column. Product purity 98.7%.

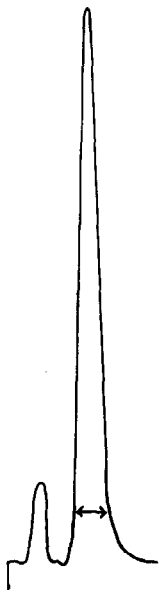


Fig. 14. Separation of 520 g of herbicide on a  $62 \times 15$  cm I.D. column of Sorbsil C30 ( $20\text{--}40 \mu\text{m}$ ). Eluent, ethyl acetate-hexane (25:75) at  $2000 \text{ ml min}^{-1}$ ; back-pressure, 20 bar; chart speed,  $180 \text{ mm h}^{-1}$ ; injection volume, 6 l. Product fraction collected between arrows. Throughput  $1.5 \text{ kg/h}$ .

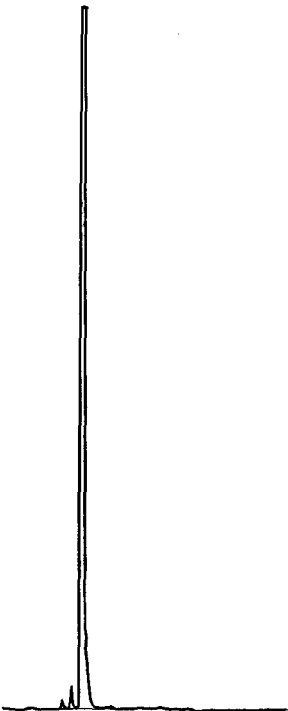


Fig. 15. Analysis of product fraction collected between arrows in Fig. 14 from application of 520 g of herbicide on a Sorbsil C30 ( $20\text{--}40 \mu\text{m}$ ) column. Product purity 98.8%.

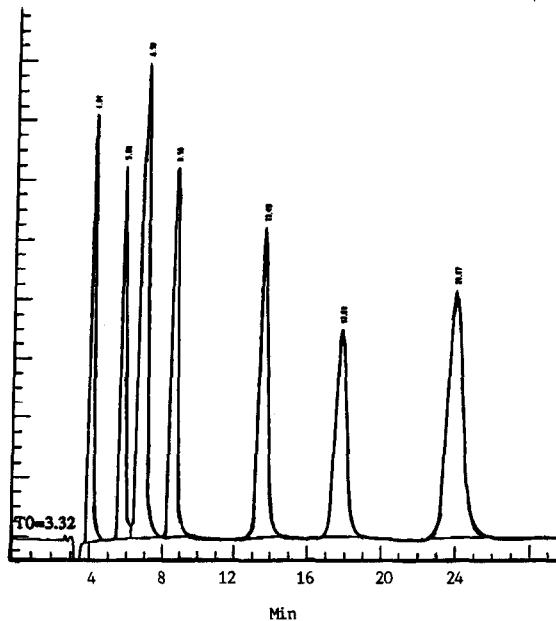


Fig. 16. Separation of test mixture on a  $21 \times 15$  cm I.D. Prochrom column packed with Sorbsil C60 ( $15\text{--}20 \mu\text{m}$ ). Eluent, ethyl acetate-hexane (10:90) at  $1000 \text{ ml/min}^{-1}$ .

variable costs. The three examples cover the following operating conditions: (1) large-particle ( $40\text{--}60 \mu\text{m}$ ), low-pressure system with the material used once and then discarded with a low solvent consumption,  $k' \approx 2$ ; (2) as (1) but with multiple use of the material and a higher solvent requirement due to column washing step between runs; and (3) small-particle ( $15\text{--}20 \mu\text{m}$ ), high-pressure system with multiple use of the material.

*Plant savings.* In a "green-field" site, considerable savings can be made owing to the reduction in the total amount of solvent which needs processing. Storage tanks, solvent pumps, chromatographic column, solvent recovery plant and sample recovery unit can all be sized smaller, leading to savings in both fixed and variable costs. At an estimated 20% reduction in plant costs resulting from a 50% increase in media loading capacity, and a plant cost of \$3 million, the capital saving would be \$600 000 with proportionate savings on depreciation and cost of capital. If buildings and facilities for solvent handling already exist, the scope for capital savings

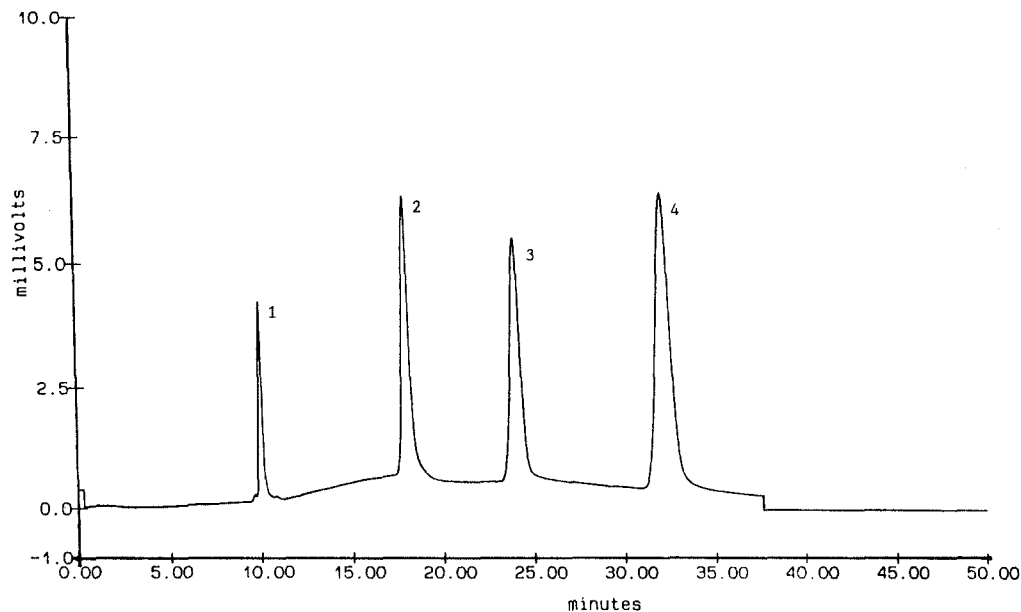


Fig. 17. Separation of toluene (1), nitrobenzene (2), phenyl acetate (3) and acetophenone (4) on a  $30 \times 10$  cm I.D. CEDI cartridge column of Sorbsil C60 (15–20  $\mu\text{m}$ ). Eluent, ethyl acetate–hexane (3:97) at  $200 \text{ ml min}^{-1}$ .

are proportionately reduced, but can still be significant.

For current processes, Sorbsil C30 offers increased throughput at no additional capital cost. Although the prime benefit is one of lower operating costs, the high capacity gives additional benefits: the concentrations of fractions are higher and lead to a reduction in the contamination of the purified material from solvent-borne impurities; and the total amount of media and solvent used will be reduced and hence the environmental impact will be minimized. This impact results from solvent and media disposal, loss of solvent to the atmosphere and the energy input into the raw materials and the separation process. Although the reduction in impact by use of a 30-Å material will not be large compared with the total environmental impact of the whole manufacturing site, significant improvements in total discharges will result from the sum of large number of smaller steps taken by individual units.

#### CONCLUSIONS

This paper has demonstrated that, contrary to popular belief, silicas of small pore size can exhibit excellent mass transfer kinetics provided that the pore-size distribution does not contain a significant proportion of micropores of less than 20 Å. Sorbsil C30 has such a pore-size distribution and, owing to its high surface area and high packing density, it is capable of significantly increasing the loading capacity per unit column volume in preparative chromatography. This improved capacity can be used to increase the capacity of an existing plant or to decrease the size of plants at the design stage. Either way, processing costs are reduced primarily through the reduction in solvent consumption and reprocessing. A material of pore size 30 Å appears to be the optimum for preparative adsorption chromatography with solute molecular weights of <1000.

## ACKNOWLEDGEMENTS

We acknowledge the provision of the data on the CEDI system by Dr. N. Herbert of Jones Chromatography (Hengoed, Wales, UK).

## APPENDIX

Assume a 50% higher loading capacity for Sorbsil C30 and we require same sample throughput per annum.

A 1000-kg amount of 60-Å material occupies 1818 l of empty column ( $\rho_p = 0.55 \text{ g ml}^{-1}$ ), which at a porosity of 0.76 needs 1380 l of solvent per unit column volume.

Owing to the increased capacity of Sorbsil C30:

660 kg of Sorbsil C30 = throughput to 1000 kg of 60-Å material and

660 kg of Sorbsil C30 occupies 1047 l of column ( $\rho_p = 0.63 \text{ g ml}^{-1}$ ), which at a porosity of 0.72 needs 754 l of solvent per unit column volume.

Examples:	1	2	3
	40-60- $\mu\text{m}$ silica, solvent not recycled	40-60- $\mu\text{m}$ silica, solvent not recycled	15-20- $\mu\text{m}$ silica, solvent recycled
No. of samples before column replacement	1	150	50
No. of column volumes per run	6	15	15
Solvent cost (\$/l)	5	5	0.5
Volume of solvent (l)	8280	1 035 000	1 035 000
Sorbsil C30 (l)	4524	565 500	565 500
Solvent costs:			
60 Å	US\$ 41 250	US\$ 5 175 000	US\$ 517 500
Sorbsil C30	US\$ 22 620	US\$ 2 827 500	US\$ 282 750
Solvent savings p.a.	US\$ 18 630 = 45%	US\$ 2 347 500 = 45%	US\$ 234 750 = 45%
<i>Media costs</i>			
1000 kg of 60-Å material	US\$ 29 000	US\$ 29 000	US\$ 200 000
660 kg of Sorbsil C30	US\$ 23 000	US\$ 23 000	US\$ 200 000
Saving p.a.	US\$ 6 000	US\$ 6 000	—
Total savings p.a.	US\$ 24 000 = 34%	US\$ 2 353 000 = 45%	US\$ 234 750 = 33%

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