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OPTIMUM USE OF PAPER, THIN-LAYER AND GAS–LIQUID CHROMATOGRAPHY FOR THE IDENTIFICATION OF BASIC DRUGS

III. GAS–LIQUID CHROMATOGRAPHY

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SUMMARY

The concept of discriminating power has been applied to the gas–liquid chromatography of 62 basic drugs using eight stationary phases which show a wide range of polarity and are representative of those in current use. The SE-30 and OV-17 columns possessed the highest discriminating powers and SE-30 was the only phase which eluted all the drugs studied. More polar columns not only failed to elute many drugs altogether but the retention indices of those that were eluted also showed high correlation with all the other columns. A single low-polarity phase, such as SE-30 or OV-17, is recommended as the "preferred liquid phase" for the identification of basic drugs. If only low-molecular-weight drugs are considered, DEGS/KOH is recommended as the second "preferred liquid phase". The use of derivatisation for the identification of basic drugs by gas–liquid chromatography is briefly discussed.

INTRODUCTION

Many stationary phases have been, and still are, used in gas–liquid chromatography (GLC). In the years 1968–1969 Preston[1] found that approximately 300 different liquid phases were cited. This is not surprising considering that Applied Science Laboratories Inc. alone offer 245 stationary phases for sale[2]. The situation does not improve even when a small chemical class of compounds is examined —as many as 210 polysiloxanes have been used as phases at one time or another[3]. It might be expected that for the analyses of toxicological extracts only a few stationary phases would have been used. Unfortunately this is not the case, and Sunshine lists 172 stationary phases in his *Handbook of Analytical Toxicology*[4].

Two monographs[5,6] deal specifically with the gas chromatographic analyses of drugs, but do not discuss which systems are the most effective for their analyses. Some authors have developed systems for the analysis of basic drugs using more than one column[7–10] and standard analytical textbooks also quote retention data using several columns[4,11].

In spite of there being so many stationary phases available, only a handful have been extensively used for the analysis of drugs, with SE-30 being the most

popular[7–10,12] and also one of the first phases to be used[13]. The other popular non-polar phase that has been widely used is Apiezon L[7,14]. Of the polar phases, Carbowax 20M has been the most popular[7,8,11,15], with CDMS also being used by some workers[16–18]. To overcome the limitations of single stationary phases, mixtures have been used with varying degrees of success, *e.g.* SE-30–Carbowax 20M[19] and Hallcomid M-18–Carbowax 600[10]. Columns have even been prepared with different stationary phases in different parts of the column, *e.g.* ethylene glycol adipate in the middle with SE-30 at both ends[20].

To overcome the difficulty with the large number of phases in use it has been suggested that "preferred liquid phases"[1] be designated and that all future work should be carried out using them, and further that systems already in existence should be modified to incorporate these phases. The designated phases include some of those already in use in systems for the analysis of basic drugs, *viz.* SE-30, Apiezon L, polyethylene glycol 20M, and DEGS[21]. The above phases were examined, together with OV-17 and CDMS, which are also often used in toxicological analyses, thus obtaining a good range of column polarity, to determine which stationary phases are the most suitable for the identification of basic drugs.

EXPERIMENTAL

Materials

The stationary phases were obtained from the following sources: SE-30 (Silicone GE SE-30, GC grade) from Supelco (Bellefonte, Pa., U.S.A.); Apiezon L, OV-17, and Carbowax 20M from Perkin-Elmer (Beaconsfield, Bucks., Great Britain); CDMS (cyclohexane–dimethanol succinate, HI-EFF-8BP) from Applied Science Labs. (State College, Pa., U.S.A.), and DEGS (diethylene glycol succinate, LAC-3-R-728) from Cambridge Industries (Watertown, Mass., U.S.A.).

Choice of basic drugs

This was made on the same basis as before[22], except that only 62 drugs were chosen.

Preparation of samples

The bases were dissolved in ether or chloroform, or extracted from aqueous solutions of their salts after the solution had been made alkaline, to give final concentrations of approximately 1 μg/μl. Solutions of the compounds for the determination of McReynolds' constants[23] were made at a concentration of 10 μg/μl. Hydrocarbon standards were dissolved in hexane or toluene to give solutions of 1 μg/μl and 10 μg/μl.

Gas chromatography

Perkin-Elmer Model F11 and Pye Model 104 (Pye-Unicam, Cambridge, Great Britain) gas chromatographs were used with flame ionisation detectors and either 1- or 2-m columns. The stationary phases shown in Table I were coated on Chromosorb G (acid-washed, DMCS-treated, 80–100 mesh).

McReynolds' constants[23] were determined for each column with 10-μg

TABLE I
GLC SYSTEMS STUDIED

Column	*Stationary phase**	*Column length (m)*	*Maximum operating temperature (°C)*
SE-30	2% SE-30	2	350
Apiezon L/KOH	2% Apiezon L +5% KOH	2	300
OV-17	5% OV-17	1	350
Carbowax 20M/KOH	1% Carbowax 20M +5% KOH	1	230
Carbowax 20M	1% Carbowax 20M	1	230
CDMS	1% CDMS	2	230
DEGS/KOH	1% DEGS +5% KOH	1	190
DEGS	1% DEGS	2	190

* On Chromosorb G (acid-washed, DMCS-treated, 80–100 mesh).

quantities of compounds, and 1-μg quantities of drugs and hydrocarbons were used for the determination of the retention indices of the drugs[24].

Treatment of results

The discriminating power[25] was calculated for each column using error factors of 10, 30, and 50 retention index units and then the discriminating power for each pair of columns was calculated using an error factor of 30 for SE-30, Apiezon L/KOH, and OV-17 and 50 for the remaining systems. Solely for the purpose of calculating the discriminating power, those drugs that failed to elute from a particular column were assigned a unique retention index. Correlation coefficients were also calculated for each pair of columns. Any drugs giving multiple peaks were excluded from the calculations.

RESULTS AND DISCUSSION

The columns examined are given in ascending order of polarity in Table II.

TABLE II
McREYNOLDS' CONSTANTS (ΔI) FOR THE GLC SYSTEMS STUDIED

Column	*Retention index of solvent*					ΔI*
	Benzene	*2-Pentanone*	*Butanol*	*Nitropropane*	*Pyridine*	
SE-30	650	680	690	710	740	249
Apiezon L/KOH	658	697	740	675	752	301
OV-17	740	796	755	896	887	853
Carbowax 20M/KOH	759	808	999	1006	945	1296
Carbowax 20M	819	872	1053	1042	1038	1603
CDMS	840	915	1006	1058	1072	1670
DEGS/KOH	1001	1038	1172	835	952	1777
DEGS	968	1021	1129	1197	1207	2301

* Calculated by summing the retention indices of the five solvents for each column and subtracting from it the sum of the retention indices of the same solvents on a squalane column (Σ=3221).

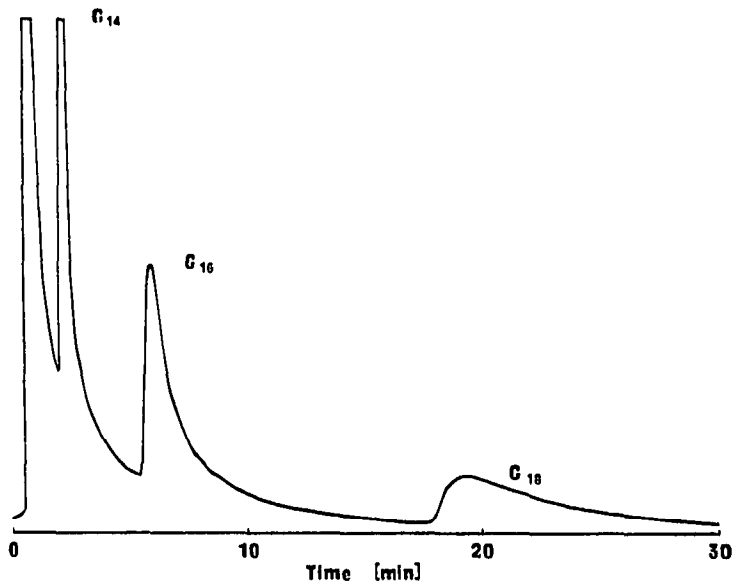

Fig. 1. Chromatogram of hydrocarbon standards (1-μg quantities) on a 2-m 1% DEGS column at 80°.

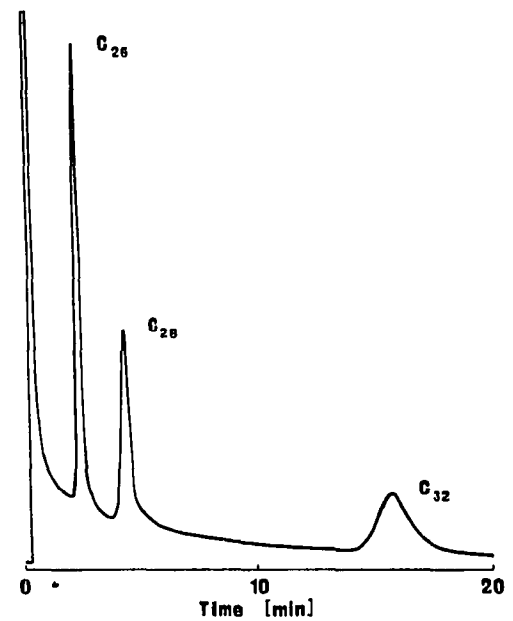

Fig. 2. Chromatogram of hydrocarbon standards (1-μg quantities) on a 2-m 1% DEGS column at 150°.

They represent the maximum range in polarity of stationary phases suitable for the analysis of basic drugs and can be divided into three groups: the non-polar, SE-30 and Apiezon L; the semi-polar, OV-17 and Carbowax 20M; and the polar,

CDMS and DEGS. Although there are more polar phases than DEGS, it is the most polar phase that can be used up to a temperature of 190°.

Of the compounds eluted from the columns, most give symmetrical peaks indicating a minimum of adsorptive action, but a temperature of at least 100° is required for the polar columns before they act as good stationary phases. Even the hydrocarbon standards tail badly on the DEGS column at 80° (Fig. 1) and it is not until the temperature of the oven is above 120° that the column gives symmetrical peaks for the hydrocarbons (Fig. 2). This feature obviously limits the useful range of the polar columns, especially since they also tend to have lower maximum operating temperatures (Table I).

The retention indices of the 62 drugs studied on the eight columns are given in Table III, together with information regarding their stability during chromatography. Some drugs give small peaks with 1-μg quantities, but disproportionately

TABLE III

RETENTION INDICES OF 62 BASIC DRUGS IN EIGHT GLC SYSTEMS

— Indicates that no peak was seen between 1000 and 3500 retention index units.

Drug	*Stationary phase*							
	SE-30	*Apiezon L/KOH*	*OV-17*	*Carbowax 20M/KOH*	*Carbowax 20M*	*CDMS*	*DEGS/KOH*	*DEGS*
Amitriptyline	2200*	2216	2550*	2788	2924	—	—	—
Amphetamine	1110*	1136	1300*	1475	1587	1694	1507	1729
Amylocaine	1574	1579	1773	1915	2029	1985	1848	2183
Antazoline	2330*	2383	2820*	—	—	—	—	—
Atropine	2048**	2012	2310	2506	2658	2650	2527	3695§
Bromodiphenhydramine	2150*	2180	2465*	2792	2942	2842	2296	3268
Butacaine	2471	—	2826	—	3646	—	—	—
Caffeine	1810*	1980	2265*	—	2941	2873	2607	3587
Carbinoxamine	2052	2070	2398	2735	2903	—	2460	3270
Carbromal	1500*	1451	1790*	1735	1844	2158	2366§	2261
Chlorcyclizine	2215*	2324	2535*	2848	2965	—	—	3310
Chlordiazepoxide	2780*	3164	3140*	—	—	—	—	—
Chlorpheniramine	2000*	2021	2285*	2577	2725	2786	2126	3031
Chlorphentermine	1320*	1360	1530*	1710	1829	1931	1673	2113
Clemizole	2680	—	3135	—	—	—	—	—
Cocaine	2180*	—	2625*	—	—	—	—	3429
Codeine	2385*	—	2820*	—	3567	—	—	—
Colchicine	3340	—	—	—	—	—	—	—
Cyclizine	2010*	2036§	2350*	2516	2664	2652	2053	2972
Dextropropoxyphene	2180*	1793§,§§ 1855	2465*	2634	2818§§ 3194 3343 3701	—	2505	3052
Diamorphine	2615*	—	3050*	—	—	—	—	—
Diazepam	2407	—	2930	—	—	—	—	—
Diethylpropion	1480*	1487§	1705*	1845	1906	1915	1827	2145
Dihydrocodeinone	2411	—	2962	—	—	—	—	—

(*Continued on p. 24*)

TABLE III (*continued*)

Drug	*Stationary phase*							
	SE-30	*Apiezon L/KOH*	*OV-17*	*Carbowax 20M/KOH*	*Carbowax 20M*	*CDMS*	*DEGS/KOH*	*DEGS*
Diphenhydramine	1855*	1877	2135*	2377	2513	2470	2047§	2817
Dipipanone	2467	2466	2821	—	—	—	—	—
Ephedrine	1350*	1360	1590*	1965**	2082	2102	2284§	2378
Ethoheptazine	1844	1827	2111	2328	2453	2425	2204	2772
Levallorphan	2340	—	2747	—	3665	—	—	3881
Lysergide	3445*	—	—	—	—	—	—	—
Meclozine	3050*	3147	3490*	—	—	—	—	—
Mephentermine	1240*	1255	1400*	1502	1602	1617	1478	1752
Meprobamate	1790*	—	2185*	1941	1981	1803	—	2199
Mepyramine	2204	2228§	2585	2970§	3134	—	—	—
Mescaline	1690*	1964§	2030*	2457§, §§ 2652	2638	—	2674	—
Methadone	2170*	2105	2445*	2609	2794	2811	2288	3043
Methaqualone	2095	2182	2553	3050	3227	—	2746	3630
Methyl-amphetamine	1170*	1182	1340*	1461	1590	1635	1400	1687
Methyl phenidate	1780*	1786§	2060*	2260	2385	2301	2182	2769
Morphine	2435*	—	2950*	—	—	—	—	—
Nicotine	1340*	1382§	1540*	1658	1814	1855	1676	2064
Nikethamide	1500*	1474***	1840*	2142	2294	2220	2344	2648
Nitrazepam	2674	—	—	—	—	—	—	—
Nortriptyline	2214	2275	2548	2899§	3062	—	—	3645
Orphenadrine	1927	1921	2195	2423	2562	2527	2109	2628
Papaverine	2806	—	—	—	—	—	—	—
Pethidine	1740*	1720	2000*	2144	2332	2256	2118	2517
Phenacetin	1660*	1661	2035*	1996§	2107	1966	—	2697
Phenazone	1830*	2237	2310*	2934	3082	—	3195	3643
β-Phenethylamine	1120*	1110	1310*	1497	1622	1856	1435	1822
Pheniramine	1802	1796§	2100	2339	2469	2538	1990	2782
Phenmetrazine	1430*	1482§	1670*	1974§	2089	2058	1723	2132
Phentermine	1130*	1170	1310*	1467	1566	1675	1493	1706
Phenylephrine	2158	—	2603	—	—	—	—	—
Phenyl-propanolamine	1310*	1332§	1500*	2046	2231	2154	—	2217
Procaine	1995*	—	2410*	—	3250	3016	—	—
Pyrrobutamine	2430*	2497	2830*	—	3270	—	—	—
Quinine	2755*	—	3300*	—	—	—	—	—
Strychnine	3040*	—	3760*	—	—	—	—	—
Thonzylamine	2045*	2183	2585*	2935	3095	—	2480	3478
Tripelennamine	1960*	1999	2300*	2540	2682	2713	2109	3019
Tryptamine	1710*	1712	2140*	—	—	—	2430	—

* Data from Kazyak and Permisohn[9].

** Major peak.

*** Nikethamide consistently gave a value of 1646 on another of our Apiezon L/KOH columns.

§ Result with 10-μg samples.

§§ Approximately equally sized peaks were obtained.

larger peaks with 10-μg quantities, indicating that some partial on-column decomposition takes place. Other drugs give minor peaks as well as a large major peak, and in these cases decomposition either in solution or in the injection port is indicated. Both dextropropoxyphene and mescaline give more than one major peak and therefore all the peaks are listed in Table III. In fact, these decompositions are so characteristic of these two compounds that they can provide a useful aid to identification.

For a column to be of the maximum use in an analysis, it should obviously elute all the drugs under consideration before its maximum operating temperature is reached. Only the SE-30 column achieves this, followed by the OV-17 column, which elutes 58 of the 62 drugs studied. The other columns show varying degrees of success, with the CDMS and DEGS/KOH columns eluting only about half of the drugs (30 and 33 drugs, respectively).

Several observations can be made from the distribution of the retention indices of the drugs on the columns used (Fig. 3). The more polar the column, the higher the retention index of the first drug to be eluted, *e.g.* the first drug to elute from the SE-30 column has a retention index of 1110, whereas the first to elute on the most polar column (DEGS) has a value of 1687. In practice the operating conditions of all the columns, *i.e.* percentage of stationary phase, length of column, etc., are always adjusted so that the first drug to be eluted from that column does so at the minimum operating temperature, thus allowing the maximum operating temperature range to be used for each column. However, because of the lower temperature maxima of the polar columns, their temperature range of operation is considerably less than that of the non-polar columns. Polar phases are therefore much less useful for the screening of extracts for basic drugs.

The number of compounds eluted by the KOH-treated columns is less than the number eluted from the non-treated columns. It has been common practice for many years to coat supports with KOH before the application of stationary phases for the analysis of basic drugs[26,27] in order to reduce the adsorptive effects of the supports. Although it does have this effect it also prevents the elution of any of the phenolic bases, *e.g.* morphine, by converting them to their non-volatile potassium phenates. Many alkaloids, especially those of high molecular weight, become thermolabile under alkaline conditions and do not elute from the KOH-treated columns (Apiezon L, Carbowax 20M and DEGS). This on-column decomposition occurs to a much lesser extent on the non-KOH-treated columns, as can be seen from Fig. 3, where the maximum retention index obtained on the Carbowax 20M column is 3700 but only 3100 on the KOH-treated column because of the non-elution of the higher molecular weight compounds.

The reproducibility of the retention indices on the columns generally decreases with increase in polarity. On individual columns operated at one temperature, the indices are always within ± 10 on the non-polar and slightly polar columns (SE-30, Apiezon L/KOH and OV-17) and within ± 25 on the more polar columns. However, when different columns using the same stationary phase are prepared, the reproducibility of the non-polar columns remains at ± 10, but the more polar columns, *e.g.* DEGS, give much more variance of retention indices. This lack of reproducibility is more noticeable at lower temperatures, *e.g.* a variation of 237 retention index units was obtained for β-phenethylamine on two DEGS/KOH

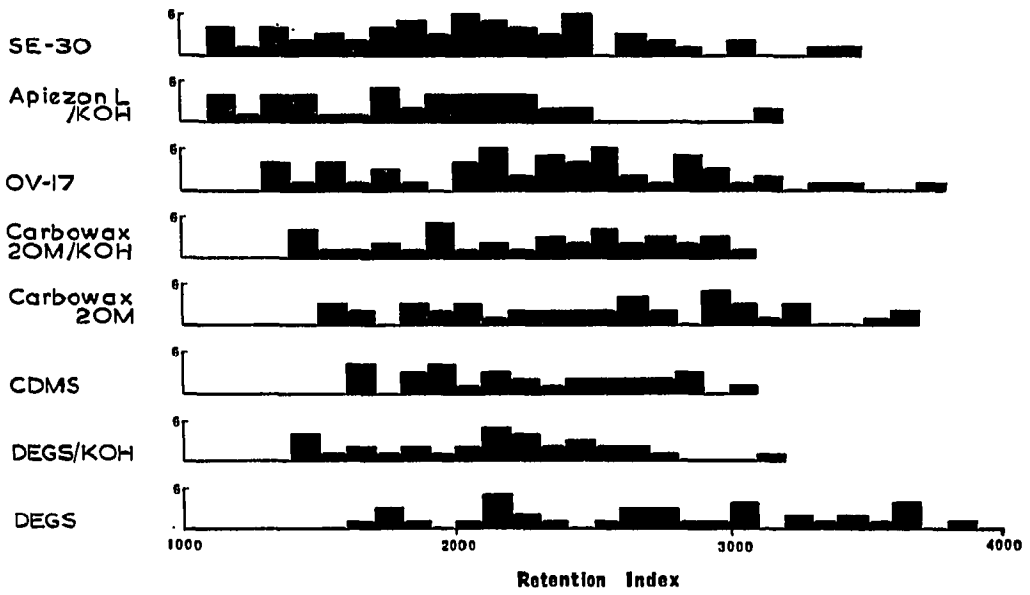

Fig. 3. Frequency distribution of retention indices of some basic drugs on GLC columns of different polarities.

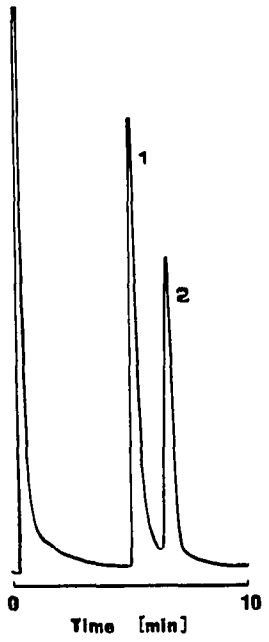

Fig. 4. Chromatogram of chlorphentermine (1) and diethylpropion (2) (retention indices 2113 and 2145, respectively) on a 2-m 1% DEGS column at 120°.

TABLE IV

DISCRIMINATING POWERS FOR SINGLE GLC SYSTEMS AT VARIOUS ERROR FACTORS

Total number of possible pairs = 1770.

Column	*Error factor (in retention index units)*		
	10	*30*	*50*
SE-30	0.987	0.967	0.945
Apiezon L/KOH	0.908	0.899	0.885
OV-17	0.983	0.971	0.953
Carbowax 20M/KOH	0.840	0.834	0.824
Carbowax 20M	0.911	0.898	0.890
CDMS	0.753	0.749	0.745
DEGS/KOH	0.766	0.760	0.756
DEGS	0.855	0.847	0.837

columns. However, most of the values can be reproduced within ± 50 provided that the column operating temperature is greater than 120°. Even when data are obtained using temperature programming (methylene units[28]), the differences between the retention indices and the methylene units $\times 100$ are never greater than ± 50.

When the data obtained in this study are compared with previously published data on the retention indices of drugs, very good agreement is found. The SE-30 results[9] are all within ± 36 and, provided that a linear regression equation is used with which to compare the data, variations of less than 26 are obtained for Apiezon L/KOH columns and less than 56 for Carbowax 20M/KOH columns, whether they are packed or support-coated open tubular columns[29].

From the above it is reasonable to assume that an appropriate error factor (E) for the SE-30, Apiezon L/KOH and OV-17 columns is 30, but that this is increased to 50 for the other columns. (Fig. 4 shows that on a single isothermal run on a polar column peaks that are separated by only 32 units can easily be distinguished and, provided all analyses are made at a single temperature, the error factor for polar columns may be reduced to 30.)

At the estimated error factors the column with the highest DP is OV-17 (DP=0.971), closely followed by SE-30 (DP=0.967). These values are very near to the maximum DP for a column of useful range, 1000–4000 retention index units, which is 0.980 at an error factor of 30 (ref. 25). The remaining columns have a much lower value for DP (Table IV). The variation in DP can be mainly attributed to the number of compounds that each column eluted. For example, the OV-17 and SE-30 columns eluted nearly all the drugs, whereas the CDMS column eluted only 30 and it therefore has the lowest value (DP=0.745). In the calculation of DP, drugs which did not elute were assigned a unique retention index so that they were all indistinguishable from each other but distinguishable from all those which did elute. Unlike the situation with PC and TLC[22], the DP does not change rapidly with variation in E. This arises principally because E is always small compared to the total range of possible retention indices. All the columns also have good

TABLE V

DISCRIMINATING POWERS FOR PAIRS OF GLC SYSTEMS

Error factor for SE-30, Apiezon L/KOH and OV-17 = 30 units; error factor for remaining columns = 50 units. Total number of possible pairs = 1770.

System	*System*						
	Apiezon L/KOH	*OV-17*	*Carbowax 20M/KOH*	*Carbowax 20M*	*CDMS*	*DEGS/KOH*	*DEGS*
SE-30	0.990	0.992	0.989	0.993	0.985	0.984	0.990
Apiezon L/KOH		0.990	0.919	0.951	0.928	0.911	0.937
OV-17			0.983	0.988	0.981	0.984	0.985
Carbowax 20M/KOH				0.897	0.862	0.866	0.874
Carbowax 20M					0.905	0.918	0.915
CDMS						0.828	0.863
DEGS/KOH							0.864

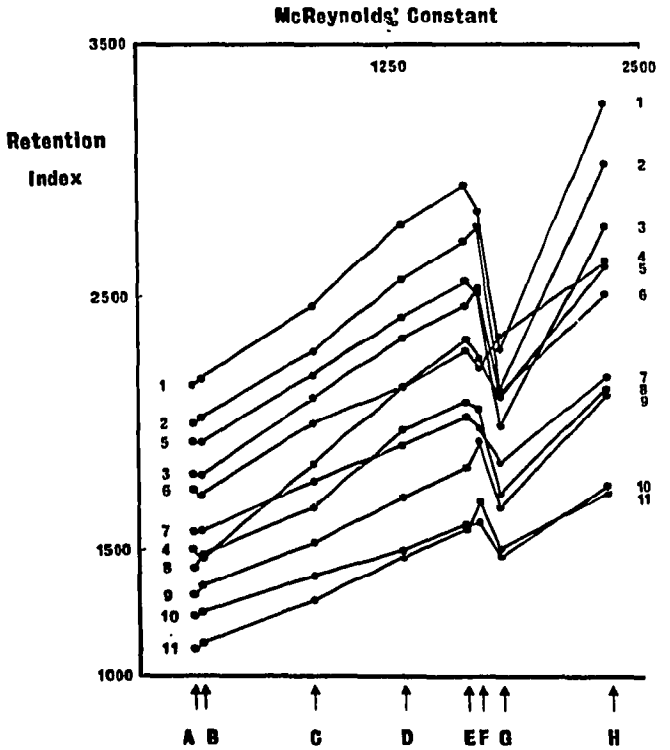

Fig. 5. Change of retention indices of some basic drugs with the polarity of the column. A = SE-30; B = Apiezon L/KOH; C = OV-17; D = Carbowax 20M/KOH; E = Carbowax 20M; F = CDMS; G = DEGS/KOH; H = DEGS; 1 = bromodiphenhydramine; 2 = chlorpheniramine; 3 = pheniramine; 4 = nikethamide; 5 = orphenadrine; 6 = pethidine; 7 = amylocaine; 8 = phenmetrazine; 9 = chlorphentermine; 10 = mephentermine; 11 = amphetamine.

frequency distributions for the peaks that are eluted —no column having more than six compounds within a band of 100 retention index units (Fig. 3).

When more than one chromatographic system is used, the combined discriminating power obviously increases and the *DP*'s for the 28 possible pairs of systems at the estimated error factors are given in Table V. The highest second order *DP*'s are associated with either the OV-17 or SE-30 systems, although they have only increased marginally from the first order *DP*'s. Nevertheless, many drug detection systems have been advocated which use both a polar and a non-polar column, such as SE-30 and Carbowax 20M/KOH[7,8,10,30]. However, as expected from the second order *DP* values, chromatographing drugs on several columns produces little extra information. Fig. 5 shows the results obtained using eleven representative

TABLE VI

CORRELATION COEFFICIENTS BETWEEN GLC SYSTEMS FOR 60 BASIC DRUGS

System	*System*						
	Apiezon L/KOH	*OV-17*	*Carbowax 20M/KOH*	*Carbowax 20M*	*CDMS*	*DEGS/KOH*	*DEGS*
SE-30	0.981	0.991	0.934	0.929	0.881	0.713	0.899
Apiezon L/KOH		0.982	0.972	0.968	0.939	0.796	0.941
OV-17			0.951	0.946	0.883	0.789	0.927
Carbowax 20M/KOH				0.999	0.964	0.849	0.963
Carbowax 20M					0.974	0.846	0.962
CDMS						0.817	0.926
DEGS/KOH							0.895

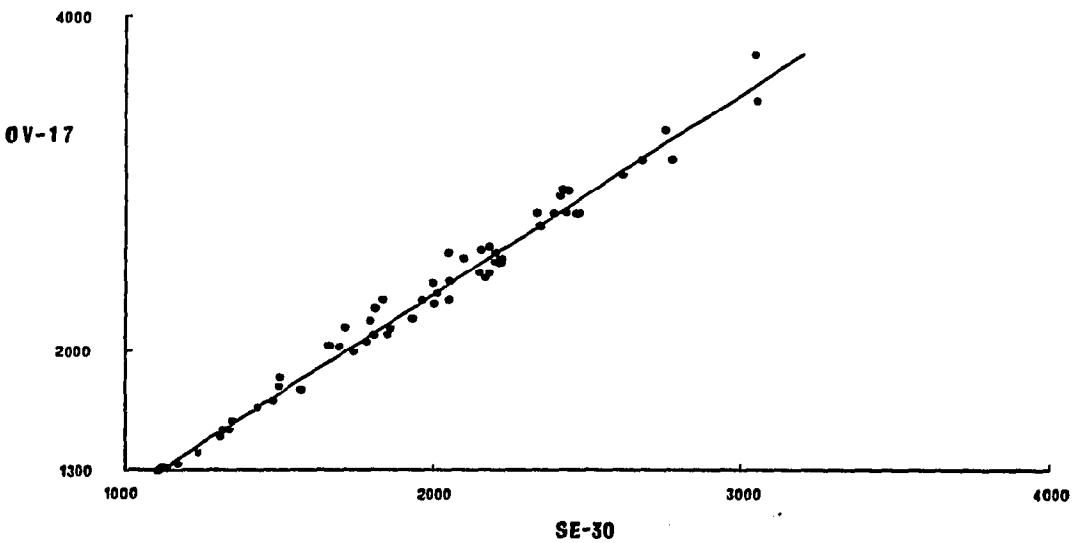

Fig. 6. Correlation of the retention indices of some basic drugs on SE-30 and OV-17 columns ($r = 0.991$).

drugs on all the columns studied. The retention indices of the drugs increase as the polarity of the column increases, but the order of elution on the least polar column is different in only two cases from that on the most polar column. Thus, all the columns exhibit similar retention behaviour to the drugs. This clearly shows that the selection of "preferred liquid phases" for basic drugs purely on the basis of polarity differences would be unwise.

The correlation coefficients (r) for each pair of phases are shown in Table VI and all the pairs are seen to be highly correlated. This explains why the second order *DP*'s have only increased marginally from the values obtained from a single low-polarity column. The highest correlation coefficient occurs for the combination Carbowax 20M and Carbowax 20M/KOH (r=0.999), followed by the two silicone phases SE-30 and OV-17 (r=0.991). Fig. 6 shows the results for the latter combination graphically and from the high degree of correlation it is obvious that if one of the columns is used for the analysis of basic drugs, the use of the second column will give very little or no additional information. Excluding the DEGS/KOH data in Table VI, the correlation is seen to be highest between non-polar and slightly polar, and also between polar and slightly polar columns. As expected, the correlation is lowest, although still highly significant, between the non-polar and polar columns.

DEGS/KOH is a special case among the phases studied, the correlation with other phases (Table VI) being much lower than would be expected purely on the basis of polarity (Table II). It is likely that the KOH treatment of the support reacts with the polyester stationary phase to modify it in such a way as to make its partition properties somewhat different from those expected. A second DEGS/KOH column was prepared using a different source of DEGS in order to check that this phenomenon was not a property of one particular column. That it is a function merely of the polyester phase can be seen from the fact that although the KOH treatment of Carbowax 20M and DEGS drastically reduces both their

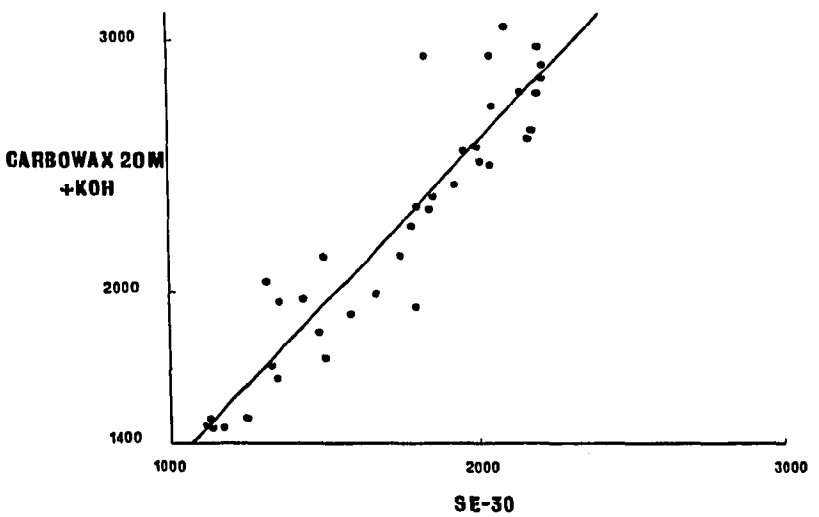

Fig. 7. Correlation of the retention indices of some basic drugs on SE-30 and Carbowax 20M/KOH columns (r=0.934).

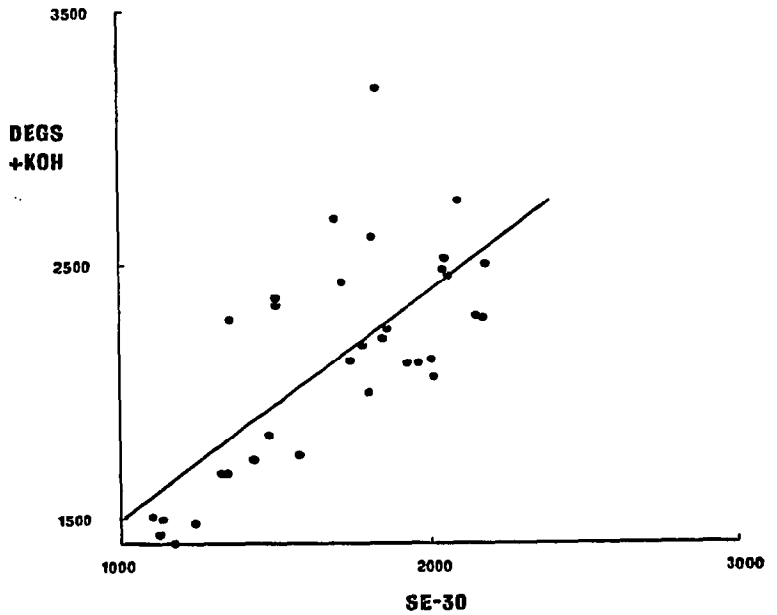

Fig. 8. Correlation of the retention indices of some basic drugs on SE-30 and DEGS/KOH columns (r=0.713).

polarities (from 1603 to 1296 and 2301 to 1777, respectively, as shown in Table II), the retention properties of the two Carbowax 20M columns are virtually identical (r=0.999), but DEGS and DEGS/KOH show distinct differences in their behaviour (r=0.895). The most popular columns used together, *viz.* SE-30 and Carbowax 20M/KOH (Fig. 7), are certainly not as good as the SE-30 and DEGS/KOH combination (r=0.713), as shown by a comparison of Fig. 8 with Figs. 6 and 7.

Derivative formation is often used as an aid to identification[6,7,10]. The fact that a derivative is formed with a particular reagent indicates the functional groups that an unknown drug may contain, and the retention indices of the derivatives provide additional data. Primary amines may be converted to Schiff bases by aldehydes or ketones, primary and secondary amines as well as phenols can be acylated by anhydrides, and alcohols and phenols can be converted to trimethylsilyl derivatives with trimethylsilylimidazole. Beckett *et al.*[7] chromatographed a number (n) of acetone Schiff bases and acetyl derivatives on both SE-30 and Carbowax 20M/KOH columns in order to identify basic drugs. On the SE-30 column the correlations between the log retention times of the base with the acetone and acetyl derivatives are 0.94 (n=11) and 0.98 (n=27), respectively, *i.e.* very little information is obtained by measuring the retention time of the product. The useful information gained is that the reaction has occurred. Chromatographing the acetone or acetyl derivatives on the Carbowax 20M/KOH column is the most useful where the correlations between the log retention times of the base and the two products are 0.49 (n=8) and 0.77 (n=14), respectively. These correlation coefficients cannot be directly compared with those in Table VI, because they are calculated in terms of log retention time instead of retention index. However, the correlation between the log retention

times on the SE-30 and Carbowax 20M/KOH columns is 0.75 (n=14) and this may be compared with the coefficient obtained from retention index data on the same columns, which is 0.934 (n=37).

Of the 62 basic drugs studied in this work, only twenty-nine would be expected to form acetyl derivatives and of these only nine are primary amines and could form Schiff bases. (The possibility of transesterification of some esters when treated with acid anhydrides or acid chlorides should not be ignored.) The formation of derivatives may therefore be used as an adjunct to the GLC analysis of basic drugs, but the retention characteristics of any reaction product are of somewhat limited value especially when the possibility of multiple derivative formation, depending on the reaction conditions used, is considered. It is of even less value when analysing large-molecular-weight drugs whose derivatives may well not elute.

It is therefore apparent that a low-polarity phase, such as SE-30 or OV-17, should be chosen as the "preferred liquid phase" for the GLC analysis of drugs. The more polar columns have much smaller *DP*'s because they fail to elute many compounds and have high error factors. The use of a second column in combination with the above would not be advocated because of the high degree of correlation characteristics which results in only a slight increase in *DP* except in the case of basic drugs having retention indices <2000 on the non-polar column, when a DEGS/KOH column could be recommended as a second "preferred liquid phase". There are insufficient data to recommend a "preferred liquid phase" for derivatisation of basic drugs. However, it is already apparent that high correlation with the retention index of the parent compound will occur using SE-30 and that only the derivatives of low-molecular-weight bases will elute on a less correlated column such as Carbowax 20M/KOH. In practice it may be preferable to use one GLC column only and then an alternative technique for further identification. For example, the combination of GLC and TLC systems might be more appropriate and this aspect will be pursued in future work.

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