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Simultaneous LC determination of paracetamol and related compounds in pharmaceutical formulations using a carbon-based column

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Abstract

A simple, rapid and convenient high performance liquid chromatographic method, which permits the simultaneous determination of paracetamol, 4-aminophenol and 4-chloracetanilide in pharmaceutical preparation has been developed. The chromatographic separation was achieved on porous graphitized carbon (PGC) column using an isocratic mixture of 80/20 (v/v) acetonitrile/0.05 M potassium phosphate buffer (pH 5.5) and ultraviolet detection at 244 nm. Correlation coefficient for calibration curves in the ranges 1–50 μg ml^{-1} for paracetamol and 5–40 μg ml^{-1} for 4-aminophenol and 4-chloroacetanilide were >0.99. The sensitivity of detection is 0.1 μg ml^{-1} for paracetamol and 0.5 μg ml^{-1} for 4-aminophenol and 4-chloroacetanilide. The proposed liquid chromatographic method was successfully applied to the analysis of commercially available paracetamol dosage forms with recoveries of 98–103%. It is suggested that the proposed method should be used for routine quality control and dosage form assay of paracetamol in pharmaceutical preparations. The chromatographic behaviour of the three compounds was examined under variable mobile phase compositions and pH, the results revealed that selectivity was dependent on the organic solvent and pH used. The retention selectivity of these compounds on PGC was compared with those of octadecylsilica (ODS) packing materials in reversed phase liquid chromatography. The ODS column gave little separation for the degradation product (4-aminophenol) from paracetamol, whereas PGC column provides better separation in much shorter time.

Keywords: Porous graphitized carbon column; Paracetamol; 4-Aminophenol; 4-Chloroacetanilide; Isocratic elution; Pharmaceutical formulations

1. Introduction

Paracetamol (acetaminophen) is a valuable non-steroidal inflammatory drug in widespread use for pain management and as antipyresis in a

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variety of patients, including children, pregnant women, the elderly, those with ostheoartheritis, simple headaches and non-inflammatory musculoskeletal conditions.

Under abnormal conditions (heat, pH, temperature, etc.) paracetamol degrades slowly forming a mixture of contaminants, such as 4-aminophenol and acetic acid [1,2]. This reaction could also be carried out by enzymatic cleavage or by microwave assisted alkaline hydrolysis [3]. In addition to 4-aminophenol, 4-chloroacetanilide could also be present as impurities in the starting material of paracetamol in which it should be controlled [4]. Therefore, it is very important to have an analytical technique for the measurement of paracetamol and its degradation product simply and precisely. A variety of high performance liquid chromatographic (HPLC) methods have been proposed for such measurement, using silica-based stationary phases [5–7]. These methods are time consuming in addition, the alkyl bonded silica-based stationary phases suffer from a number of drawbacks, including poor stability at extremes of pH and a variety of unwanted interactions due to surface heterogeneity [8]. However, due to the instability of these packing materials and the complicated separation systems, porous graphitized carbon (PGC) showed to be preferable packing for the separation and determination of drug and pharmaceuticals [9–12]. This material has several advantages, most notably its physical and chemical stability, as well as superior selectivity towards diasteriomers and geometric isomers [13] and also is most applicable to the separation of small ionisable molecules that are not retained with octadecylsiloxane (ODS) columns [14].

This work describes a simple and rapid HPLC method for simultaneous determination of paracetamol, 4-aminophenol and 4-chloroacetanilide using PGC column. This method was suitable for the quality assessment of paracetamol in pharmaceutical preparations. Further, studies were carried out on the effect of the mobile phase composition and pH in the retention of these compounds on PGC column.

2. Experimental

2.1. Chromatography (instrumentation and conditions)

The analytical separation was carried out with a gradient modular HPLC system equipped with a diode array spectrophotometer UV 168 (Beckman Instruments Inc.). A flow rate of 1 ml min^{-1} was used for the separation of paracetamol, 4-aminophenol and 4-chloroacetanilide. The column was carbon column (100×4.6 mm^2 i.d., 7 μm particle size) packed with Hypercarb PGC (Shandon, Runcorn, UK) was used for retention measurements. The mobile phase composed of two components, organic solvent and buffer solutions with different ratios and pH. The organic solvents tested were acetonitrile (ACN), methanol (MeOH) and tetrahydrofuran (THF). The ODS column (Supercosil LC-18, 250×4.6 mm^2 i.d., 5 μm particle size) was used with a mobile phase containing MeOH and buffer. The buffer composition was: 0.05 M KH_2PO_4, pH 6 and 0.01 M tetrabutyl ammonium bromide (TBA) as ion pairing agent.

2.2. Reagents

HPLC-grade ACN was obtained from Prolabo (Paris, France). LC-grade water was prepared by purifying demineralized water in a Milli-Q filtration system (Millipore, Bedford, MA). Reference standards for paracetamol, 4-aminophenol and 4-chloroacetanilide were kindly supplied by laboratory Ibn Al-Baytar (Tunis, Tunisia). Dosage forms were obtained from different local pharmacies; Pyralgan500 tablets '500 mg paracetamol', Trifed plus tablets contain 300 mg paracetamol (plus 50 mg pseudoephedrine HCl and 2.5 mg triprolidine HCl), co-codamol tablets 500 mg paracetamol (plus 8 mg codeine), Adol tablets '500 mg paracetamol' and Efferalgan '330 mg paracetamol' (plus 200 mg of vitamin C). All other chemicals were of analytical grade and were obtained from Prolabo.

2.3. Preparation of solutions

Stock solutions of paracetamol, 4-aminophenol and 4-chloroacetanilide (1 mg ml^{-1} each) were prepared in the mobile phase and stored at 4 °C. The working standards (1–50 μg ml^{-1} for paracetamol and 5–40 μg ml^{-1} for 4-aminophenol and 4-chloroacetanilide) were freshly prepared from the stock solutions by dilution with the appropriate volume of the mobile phase. Drug tablets were prepared by crushing 20 tablets and an accurately weighed portion of the mixed powder equivalent to paracetamol content of one tablet was transferred to 100 ml volumetric flask and dissolved by sonication. The sample was filtered and diluted to make a final concentration in the range of 10–20 μg ml^{-1}.

2.4. Stability studies

Initially, typical stability protocols were tested, but because the drug substance studied was found to be extremely stable, more stressful conditions were applied to yield degradation products. An amount equivalent to 100 mg paracetamol was heated with 20 ml H_2SO_4 (4 M) in a water bath at 50 °C for 30 min and the solution was cooled and diluted to 100 ml with water. To determine the hydrolysis products of paracetamol, a portion of 10 ml of the aliquot was diluted to 100 ml before injecting into the column.

3. Results and discussion

3.1. Chromatography

The baseline separation of paracetamol, 4-aminophenol and 4-chloroacetanilide was achieved on PGC column using isocratic elution and ACN as the organic modifier (Fig. 1). The analysis of these compounds on PGC was achieved in a short time with a maximum retention time of 7.05 min. In addition, the separation of these compounds was achieved, when using MeOH as the organic modifier (Fig. 2). These separation conditions are much better than the separation obtained by reversed phase ODS column (Fig. 3). Improved resolution of paracetamol from their contaminants were features with tailing factors and column efficiency within the limit recommended by Pharmacopoeia official methods [15,16]. Results obtained for chromatographic parameters are shown in Table 1. This method can be used for controlling paracetamol contaminates with better limits than that specified in the current official methods 'United States and British pharmacopoeia'. Furthermore, the separation of these compounds was achieved by using water instead of the buffer solution. However, the buffer solution was used to minimise the variation of the mobile phase pH during the analysis of drug samples.

The main advantage of PGC method is that the results (replicates of samples and standards) can be obtained rapidly. In addition, this column showed fast equilibrium with the changes in the mobile phase composition and a high stability during the analysis.

3.1.1. Effect of the mobile phase composition

The chromatographic behaviour of 4-aminophenol, paracetamol and 4-chloroacetanilide on PGC was examined under variable mobile phase compositions (nature and concentration).

The percentage of ACN content of the mobile phase can be used to control the retention of 4-aminophenol, paracetamol and 4-chloroacetanilide. The retention time of each of the three compounds was determined at several different ACN concentrations from 10 to 40% (v/v), by the replicate injections of a mixture of the three analytes with each mobile phase composition. In each case, the retention time of the three compounds decreased as the concentration of the organic modifier increased. The plots (Fig. 4) of $\log k'$ values for the three compounds against the aqueous phase concentration, when using ACN as the organic modifier, show an approximately linear relationship. Similarly Fig. 5, shows an increase in the retention factor of these compounds by decreasing MeOH concentration in the mobile phase. However, the increase in the retention factor was more notable by decreasing the concentration of MeOH than that of ACN. As an example,

at a lower ACN concentration (60%) than MeOH (80%), the retention time of 4-chloroactanilide was 5 min lower than that of MeOH. This may indicate that ACN with dipolar properties has a stronger effect on PGC than MeOH and so a smaller retention factor. Fig. 2 shows the separation of 4-aminophenol, paracetamol and 4-chloroacetanilide on PGC column using MeOH as the organic modifier.

The effect of the mobile phase was further investigated using ACN, MeOH and THF as the organic modifier and phosphate buffer (pH 5.5) as the aqueous phase. Comparing the three solvents, and in addition to its lower concentration in the mobile phase, it was found that THF shows much shorter retention times for the three compounds than ACN or MeOH (Table 2). This indicates that THF with higher dipolar properties than ACN could be used to avoid long retention times for late eluting substances.

3.1.2. Effect of the mobile phase pH

The retention of 4-aminophenol, paracetamol and 4-chloroacetanilide was further investigated by changing the mobile phase pH (Table 3). The effect of the pH upon elution of these compounds was quite different to that obtained by changing organic modifier concentrations.

The pH of the mobile phase was increased from pH 2.5 to 12 and the retention time of each of these compounds was determined at each pH value. In the range 2.5–6.0, the hydrogen ion concentration of the mobile phase appeared to have little or no effect on the solute retention,

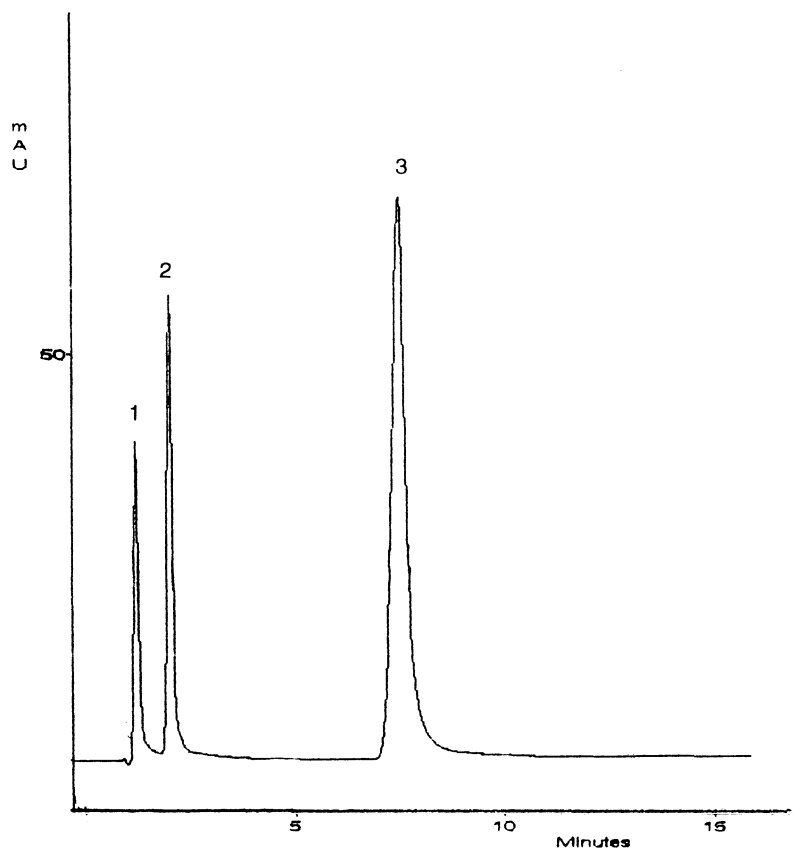

Fig. 1. Separation of 4-aminophenol, paracetamol and 4-chloroacetanilide. Chromatographic conditions: Column: Hypercarb (100×4.6 mm^2 i.d. packed 7 μm PGC); mobile phase, ACN-50 mM phosphate buffer pH 5.5 (80:20, v/v); flow rate 1 ml min^{-1}; injection volume, 20 μl; UV detection at 244 nm. Peak1: 4-aminophenol, Peak2: paracetamol, Peak3: 4-chloroacetanilide.

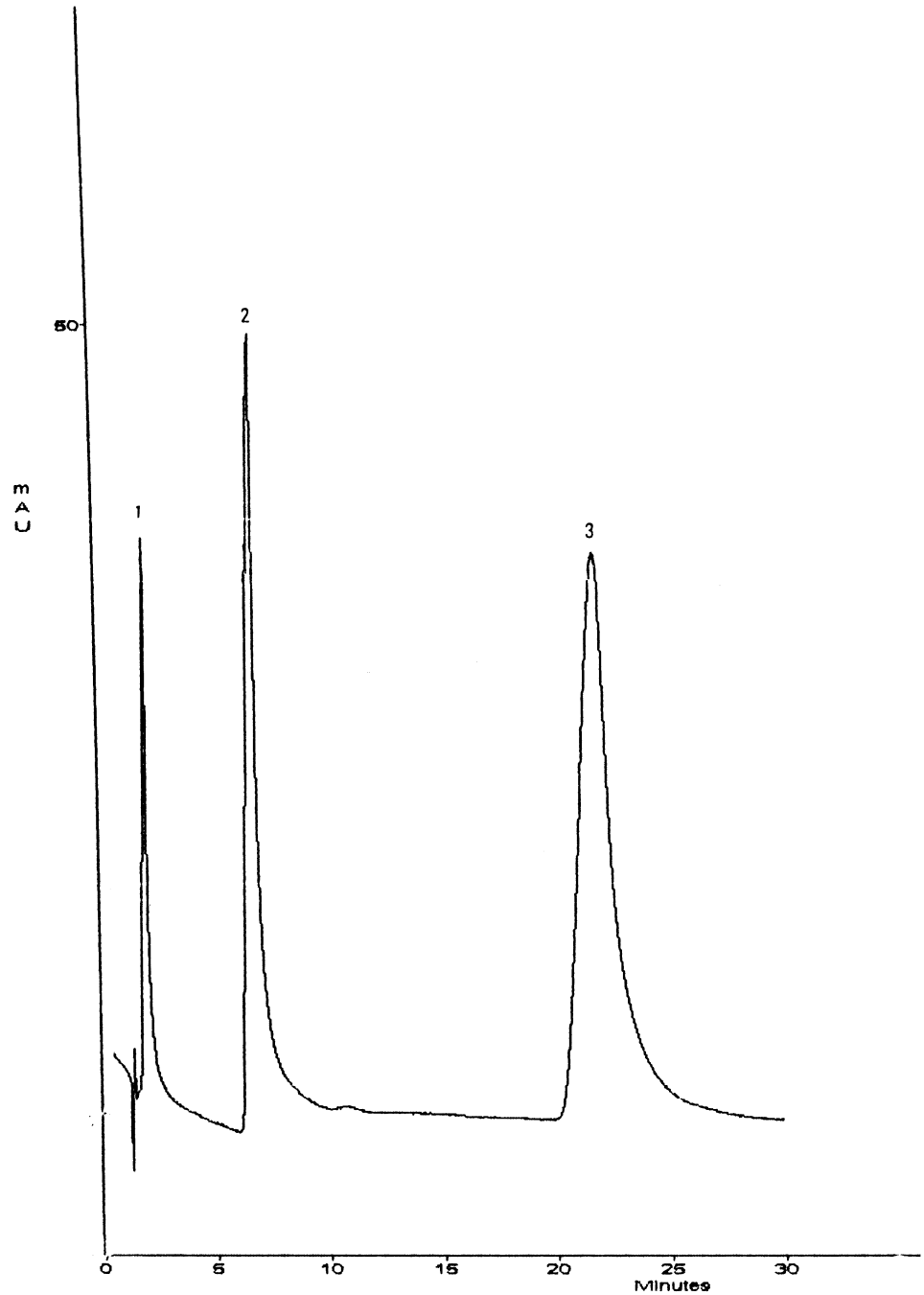

Fig. 2. Separation of 4-aminophenol, paracetamol and 4-chloroacetanilide. Chromatographic conditions: Column: Hypercarb (100×4.6 mm i.d. packed 7 μm PGC); mobile phase, MeOH-50 mM phosphate buffer pH 5.5 (80:20, v/v); flow rate 1 ml min^{-1}; injection volume, 20 μl; UV detection at 244 nm. Peak1: 4-aminophenol, Peak2: paracetamol, Peak3: 4-chloroacetanilide.

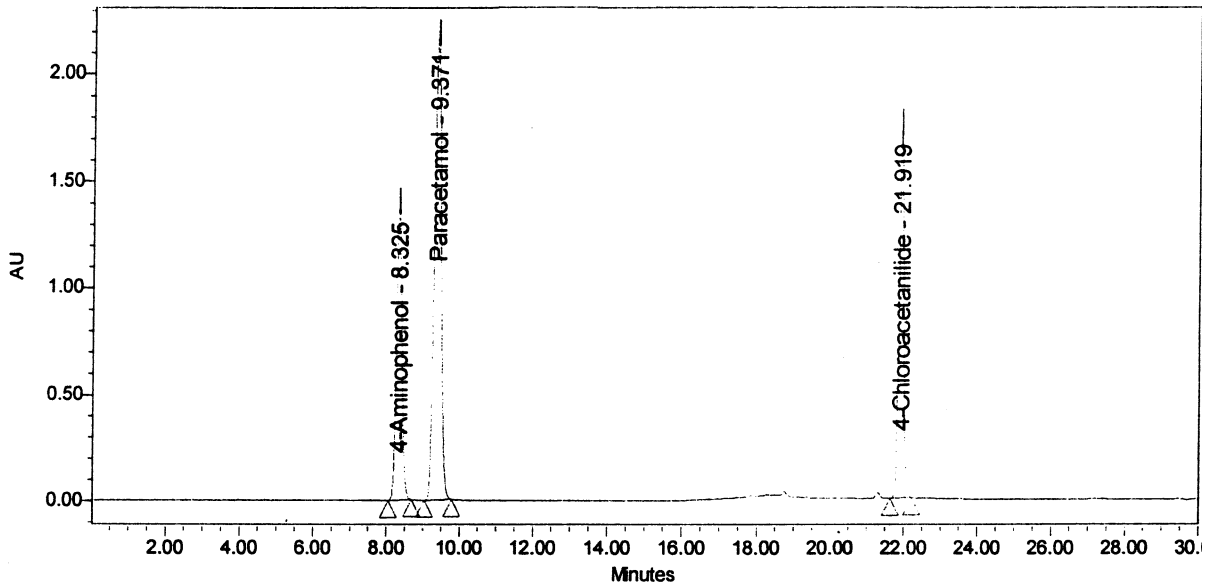

Fig. 3. Separation of 4-aminophenol, paracetamol and 4-chloroacetanilide using octadecyl silica column. Chromatographic conditions: Column: Supercosil LC-18 (250×4.6 mm^2 i.d. packed 5 μm); gradient elution, 50 mM phosphate buffer with 10 mM TBA-MeOH (started 84:16 after 11 min 40:60 buffer-MeOH); flow rate 0.8 ml min^{-1}; injection volume, 20 μl; UV detection at 244 nm. Peak1: 4-aminophenol, Peak2: paracetamol, Peak3: 4-chloroacetanilide.

however, at pH values greater than 8, the retention of 4-aminophenol and paracetamol decreased until a co-elution of the two compounds as a single peak, when reaching a pH value of 12. It is likely that the abrupt change observed is due to the changes in the state of ionisation of these compounds as the pH of the mobile phase changes. At high pH, the hydroxyl groups on 4-aminophenol and paracetamol will be deprotonated and so attracted to the aqueous mobile phase and thus compound retention will be reduced.

3.1.3. Comparison of the separation on PGC and ODS columns

The separation of paracetamol and related compounds have been compared with ODS column (Supercosil LC-18, 250×4.6 mm^2 i.d.). The ODS column gave a little separation for the degradation product (4-aminophenol) from paracetamol and a very long retention time for 4-chloroacetanilide. Therefore, a gradient elution was necessary to separate 4-aminophenol from paracetamol and to reduce the retention time of 4-chloroacetanilide. The optimum separation was obtained using an initial mobile phase composition of 16/84 MeOH-buffer and a final composition (after 14 min) of 60/40 MeOH-buffer. As shown in Fig. 3, the retention required to separate the three compounds on ODS column was greater than 21 min. The elution order of these compounds was similar to that obtained by PGC column, which indicated a similarity in the behaviour of these compounds on the two column. However, PGC column require a higher organic

Table 1
Chromatographic parameters of paracetamol and related compounds on PGC column using the optimum separation conditions; 80/20 ACN-phosphate buffer (pH 5.5)

Compounds	k'	A_s	N	R_s
4-Aminophenol	0.33	1.1	1420	
				2.1
Paracetamol	0.97	1.3	2216	
				4.2
4-Chloroacetanilide	4.88	1.6	2110	

Column size: 100×4.6 mm^2 i.d., 7 μm, concentration of buffer 50 mM.

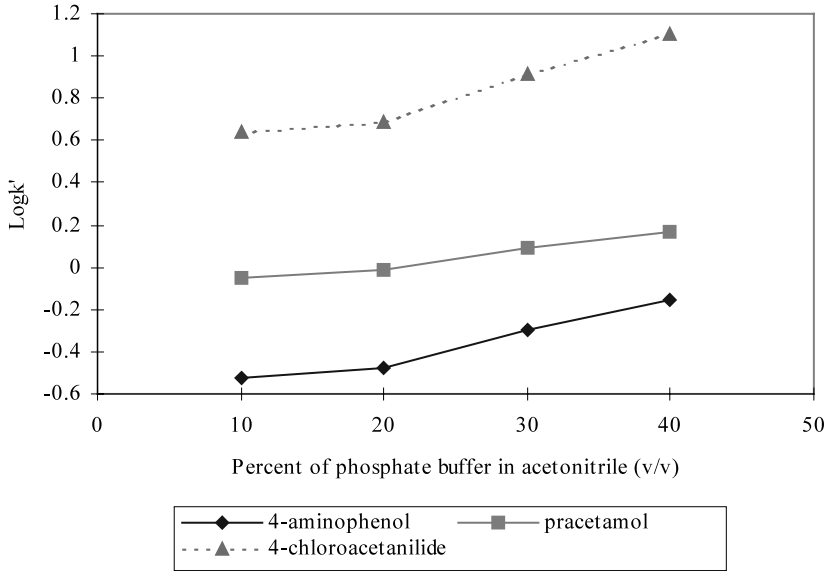

Fig. 4. Plots of the capacity factor ($\log k'$) values of 4-aminophenol, paracetamol and 4-chloroacetanilide on PGC against aqueous phase concentration (pH 5.5) using ACN as the organic modifier.

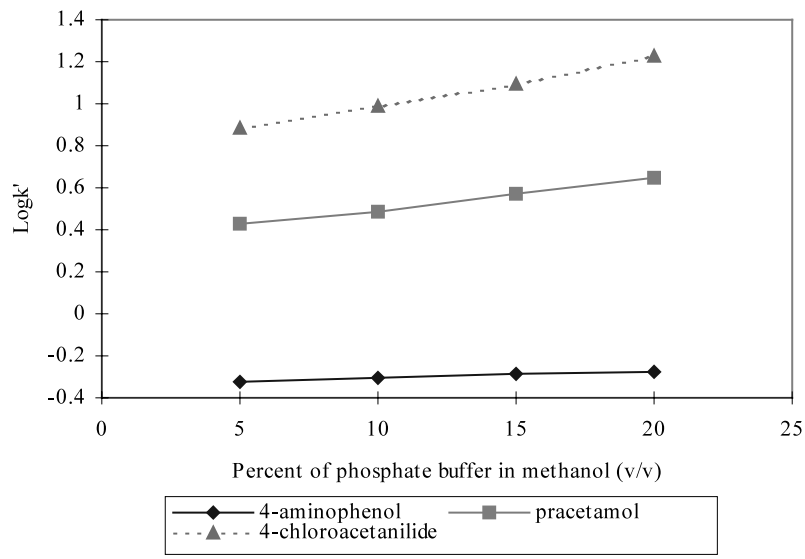

Fig. 5. Plots of the capacity factor ($\log k'$) values of 4-aminophenol, paracetamol and 4-chloroacetanilide on PGC against aqueous phase concentration (pH 5.5) using MeOH as the organic modifier.

modifier ratio than that of ODS column, which indicates that PGC is more highly hydrophobic than ODS column. These results indicate that PGC column has a higher selectivity towards the separation of compounds difficult to achieve on other revered phase columns. In addition to its high selectivity towards drugs and pharmaceuticals, PGC showed a faster equilibrium time, when changing the mobile phase composition than that of ODS materials.

Table 2
Effects of the organic modifier on the retention factors (k') of paracetamol and related compounds on a PGC column

Compounds	THF/buffer 40/60	ACN/buffer 80/20	MeOH/buffer 80/20
4-Aminophenol	0.04	0.33	0.53
Paracetamol	0.39	0.97	4.46
4-Chloroacetanilide	3.14	4.88	17.08

3.2. Validation of the analytical method

The analytical method was validated by performing a series of tests using the optimised chromatographic conditions chosen (Fig. 1).

3.2.1. Selectivity

The selectivity of the method for determination of paracetamol in the presence of degradation and related products was studied by spiking paracetamol samples with 4-aminophenol and 4-chloroacetanilide. As shown in Fig. 1, there was adequate resolution for the three compounds. The purity of paracetamol peak was verified using a diode array detector (Beckman Model 168). The selectivity was further assessed by analysis of standard solutions containing freshly prepared paracetamol and paracetamol that had been degraded after hydrolysis with 4 M H_2SO_4 for 30 min at 50 °C. The analysis of the hydrolysed sample indicates the presence of a second peak in addition to paracetamol peak. According to the retention time, this peak was corresponding to 4-aminophenol. The amount of 4-aminophenol was 20 mg l^{-1}, which indicates a reduction in the paracetamol initial concentration (100 mg l^{-1}) to 79.5 mg l^{-1}. So the proposed method is capable for resolving paracetamol from the degradation products that could be formed during hydrolysis. Therefore, it could be used as a stability-indicating procedure for paracetamol.

3.2.2. Linearity

The calibration curves for 4-aminophenol, paracetamol and 4-chloroacetanilide were constructed separately using the above mentioned conditions. The concentrations examined were between 1 and 50 μg ml^{-1} for paracetamol and between 5 and 50 μg ml^{-1} for 4-aminophenol and 4-chloroacetanilide. The correlation coefficients (R^2) of the calibration curves (peak area versus concentration) were between 0.990 and 0.999. The equations of these curves ($y = mx + b$) were then used to calculate the unknown concentrations in the paracetamol samples. The least squares linear regression analysis data are shown in Table 4.

3.2.3. Precision

The precision of the proposed method was determined by studying the within- and between-day precision (expressed as the relative standard deviation, RSD) for both retention times and peak areas by repeated analysis ($n = 6$) of 4-aminophenol, paracetamol and 4-chloracetanilide standard solution (Table 5). The within-day RSD values obtained for retention times were $< 1.0\%$ and for peak areas were between 1.3 and 2.1%. The between day RSD values obtained for retention time were 0.4–1.1 and for peak areas 1.9–3.0%.

3.2.4. Analytical recovery, reproducibility and limit of detection

The recovery assessment was performed by analysing real paracetamol samples spiked with known amounts (10 μg ml^{-1}) of 4-aminophenol, paracetamol and 4-chloroacetanilide standards.

Table 3
Effects of buffer pH on the retention factors (k') of paracetamol and related compounds on a PGC column

Compounds	pH 3.5	pH 4.5	pH 5.5	pH 12
4-Aminophenol	0.28	0.29	0.33	0.23
Paracetamol	0.92	0.96	0.97	0.23
4-Chloroacetanilide	4.55	4.67	4.88	5.05

Mobile phase 80/20 ACN/aqueous solution. Column size: 100 × 4.6 mm i.d., 7 μm, concentration of phosphate buffer 50 mM.

Table 4
Calibration curve parameters for the analysis of paracetamol and related compounds on PGC, obtained by linear regression analysis of peak area versus concentration in μg ml^{-1}

Paracetamol and related compounds	Slope	RSD of the slope (%)	Intercept	RSD of the intercept (%)	R^2
4-Aminophenol	33027	4.0	30151	5.3	0.9901
Paracetamol	122029	4.1	73059	4.9	0.9994
4-Chloroacetanilide	98420	4.8	42066	5.1	0.9904

Table 5
Reproducibility, recovery and limit of detection of chromatographic analysis of paracetamol and related compounds using isocratic elution and a PGC column

Compounds	Retention time[a] Mean ± S.D. (min)	RSD (%)	Peak area[b] RSD (%)	Recovery[c] (%)	Limit of detection (μg ml^{-1})
4-Aminophenol	1.57 ± 0.04	0.76	2.00	99.5	0.1
Paracetamol	2.36 ± 0.02	0.66	1.30	100.1	0.5
4-Chloroacetanilide	7.05 ± 0.02	0.66	2.10	98.9	0.5

[a] Chromatographic conditions as in Fig. 1.
[b] Twenty microlitre injection of 20 μg ml^{-1} solutions ($n = 6$).
[c] Twenty microlitre injection of paracetamol samples spiked with 10 μg ml^{-1} standard solutions ($n = 6$).

The recovery of paracetamol from tablets was 100.1% and for 4-aminophenol and 4-chloroacetanilide was 99.5 and 98.9%, respectively. The detection limit for the three compounds was measured by injection of 20 μl of standard solutions and the values of these compounds were between 0.1 and 0.5 μg ml^{-1} (signal-to-noise ratio of 3:1). The limit of quantification of these compounds was 0.3, 1 and 1.3 μg ml^{-1}, respectively (signal-to-noise ratio 10:1). The reproducibility of the retention times and peak areas are summarised in Table 5.

3.2.5. Robustness

The robustness of the method was evaluated by deliberate variation in the method parameters, such as pH and phosphate buffer concentration. The change in the chromatographic results of the same sample was monitored by varying these parameters, and it was found that there was little change in the resolution of the two adjacent pair of compounds as the pH changed from 3.5 to 5.5. Slight changes in the retention times of all the peaks were also noted with repeated injections. However, the peak shapes of all peaks were quite good at the different pH values. There was no significant changes in the chromatographic results with alteration in phosphate concentrations in the mobile phase.

3.2.6. Analysis of paracetamol formulations

The developed method was applied to the analysis of commercially available paracetamol containing formulations from different manufacturers. The formulations collected were treated and filtered through a 0.45 μm filter before injection. The assay was repeated six times for each type of preparation. The quantitative results of these assays are summarised in Table 6. The results demonstrated that the content of paracetamol in paracetamol formulations and paracetamol containing formulations (e.g. a mixture of Paracetamol and vitamin C formulations) correspond to each drug label. The samples were also analysed by a standard method [14] and results obtained are collected in Table 6. As can be seen, good agreement was found between the standard and the developed method. This fact shows the applicability of the developed method in pharmaceutical analysis without interference problems

Table 6
Results of the analysis of different forms of commercialised drugs using the proposed and the standard method

Commercialised formulations	Society (laboratory)	Label amount (mg paracetamol)	% Found ± S.D. ($n = 6$)	
			Proposed method	Standard method
Pyralgan	Avicenne	500	99.2 ± 1.1	98.1 ± 1.5
Adol	SAIPH	500	98.9 ± 1.6	99.0 ± 2.0
Efferalgan	UPSA	330	98.0 ± 2.0	98.0 ± 1.6
Trifed plus	Ibn Albaytar	300	102.9 ± 2.0	101.0 ± 1.6
Co-codamol	Boots	500	99.6 ± 1.5	98.6 ± 2.2

derived from other substances, which frequently attends paracetamol in analgesic formulations.

4. Conclusion

The chromatographic behaviour of 4-aminophenol, paracetamol and 4-chloroacetanilide was examined under variable mobile phase compositions and the results obtained showed that retentions were dependent on organic phase nature, concentration and pH. Stronger eluents with dipolar properties, such as THF could be used with PGC to avoid long retention times for late eluting compounds.

The specificity, precision and reproducibility of the analytical method can be used for qualitative and quantitative analysis of paracetamol in pharmaceutical products and for controlling their contaminates within the limits specified in the current official methods. The simplification of the working condition of the method reported here make it a suitable alternative to other official methods used for quality controlling of paracetamol. Furthermore, PGC column showed high retention selectivity, rapid equilibrium and a high stability during the analysis than commercially used ODS columns.

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