

# Degradation of paracetamol and other constituents in Perfalgan®

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**Background:** The manufacturers of Perfalgan®, a formulation of intravenous paracetamol, recommend that each ampoule be used once only. This is most likely due to concerns regarding degradation of paracetamol or other ingredients in the solution, and sterility issues. However, in South Africa, where the expense of this drug limits use, some centres use one ampoule for multiple paediatric cases over the course of 12–24 hours. No obvious clinical adverse effects have been reported.

**Aim:** The aim of this study was to examine this practice by assessing drug bioavailability as well as the in vitro stability of the paracetamol and excipients in Perfalgan® on exposure to air and specific stressors over time.

**Methodology:** High-performance liquid chromatography (HPLC-UV) was used to determine the concentration of paracetamol and the presence of degradation products in samples taken at set time intervals following exposure of Perfalgan® to air and stressors. Since changes in other components, or excipients, may impact efficacy, these were measured using nuclear magnetic resonance (<sup>1</sup>H NMR). The octanol:water partition coefficient was used as an indicator of bioavailability. Ultraviolet spectroscopy was used to calculate the penetration of paracetamol in Perfalgan® into the lipid layer.

**Results:** The paracetamol in Perfalgan® did not degrade on exposure to air over 24 hours. Neither did it degrade on exposure to acid, alkali, oxidative or heat stress. <sup>1</sup>H NMR revealed no change in the formulation of Perfalgan® except for the conversion of the oxygen scavenger cysteine to cystine. The octanol:water partition coefficient likewise stayed constant and was in agreement with the value of 0.46–0.49 quoted in the literature.

**Conclusion:** Paracetamol and the excipients in Perfalgan® did not degrade on exposure to air and other stressors over 24 hours. The drug retained its lipid permeability over this period.

**Keywords:** excipients, high-performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), Perfalgan®, ultraviolet spectroscopy (UV spectroscopy)

## Introduction

Oral paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity.<sup>1</sup> It has been used in the perioperative period because of its presumed opioid-sparing effect.<sup>2</sup> Until recently paracetamol was unavailable in the intravenous form due to its poor water solubility.<sup>3</sup> Improved stabilisation techniques have recently allowed development of paracetamol as an intravenous form. In South Africa intravenous paracetamol is marketed by Bristol-Myers Squibb as Perfalgan®. According to the manufacturers,<sup>4–6</sup> the main excipients are mannitol (which aids solubility), cysteine hydrochloride (preservative and antioxidant) and nitrogen as the resident gas in the vial to eliminate oxygen. Sodium phosphate, sodium hydroxide and hydrochloric acid are buffers used to maintain a pH of 5.5, minimising hydrolysis. Other intravenous paracetamol preparations exist. In North America intravenous acetaminophen (paracetamol) is marketed by Mallinckrodt Pharmaceuticals as Ofirmev®. The formulation has similarities to Perfalgan® in that it too contains 1 g of paracetamol and the main excipients are mannitol and cysteine.<sup>7</sup>

Bristol-Myers Squibb advise that Perfalgan® be infused over 15 minutes and each vial be for single use only.<sup>8</sup> No reason is given for this. Presumably there are concerns over the degradation of the product as well as sterility as the vial contains no antimicrobial agent.

Much work has been performed on the stability of oral paracetamol alone and in combination drugs, with liquid chromatography being the most widely accepted method.<sup>9,10</sup> A

PubMed search revealed limited research on intravenous paracetamol stability. Kwiatkowski, Johnson and Wagner tested samples of intravenous paracetamol with HPLC after exposure to air.<sup>11</sup> Some 99% of the initial paracetamol concentration remained when tested over a period of 84 hours. Bernard *et al.* examined intravenous paracetamol in infusion sets during the infusion and after 24 hours of stasis within the set.<sup>12</sup> Chromatographic analysis revealed paracetamol to be stable. The authors propose that successive doses of paracetamol may be infused through an administration set as the drug is stable. No work was found focusing on the stability of intravenous paracetamol on exposure to heat or other stressors, or on the excipients in Perfalgan®.

## Purpose of study

The purpose of this study was to measure the chemical and physical changes of Perfalgan® over time via three distinct components:

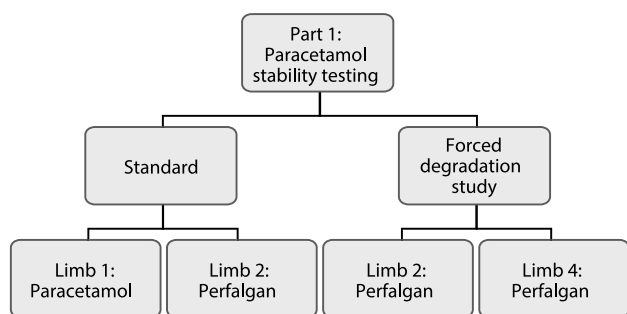
Part 1: Stability study of pure paracetamol and Perfalgan® over time.

Part 2: Stability study of excipients over time, which may impact on solubility or bioavailability.

Part 3: Bioavailability study of Perfalgan® as indicated by penetration of paracetamol into a lipid layer.

## Method

1. Paracetamol stability testing



Note: 'Standard conditions' is synonymous with 'unstressed' and 'forced degradation study' with 'stressed', as described in the text.

Figure 1: Four limbs of stability testing.

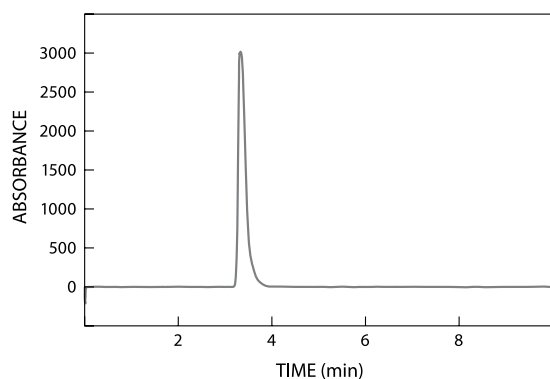


Figure 2: Chromatogram of paracetamol 513 µg.ml<sup>-1</sup> at 0 hours.

Paracetamol stability was tested under 'unstressed' and 'stressed' conditions. The 'unstressed' sample was drawn from a vial that was exposed to air, simulating normal use. This was termed standard conditions. 'Stressing' refers to placing the drug under conditions that may force it to degrade or alter its structure, namely by adding acid, alkali, or an oxidising agent and exposing to dry heat. This was termed a forced degradation study. The purpose of forced degradation was to test, in the case of no degradation of paracetamol under 'unstressed' conditions, whether it was possible to detect change under extreme conditions.

Stability testing therefore had four limbs as depicted in Figure 1.

The methodology used was derived from work performed by Shah *et al.*<sup>10</sup> Reverse-phase high-performance liquid chromatography with an ultraviolet detector (RP-HPLC, Company: Agilent, Head quarters: Santa Clara, United States of America)-UV was used to quantify paracetamol. The SpectraSERIES 200 system used a mobile phase of 0.05 M potassium hydroxide phosphate:methanol (40:60 v/v) and a Thermo Electron Corporation C18 column. Eluents were monitored at 266 nm. The retention time (tR) of paracetamol was expected to be approximately 2.7 minutes.

Limb one: paracetamol under standard conditions:

Calibration curves were created by analysing paracetamol stock solution of varying concentrations, by plotting peak area with concentration. An  $R^2$  value of better than 0.95 was regarded as acceptable. Integration of the area under the peak yielded the paracetamol concentration.

Limb two: Perfalgan® under standard conditions:

Perfalgan® stock solution was similarly analysed. The paracetamol peak was examined in a sample of stock solution at 0 hours and 24 hours.

Limb three: paracetamol forced degradation study:

According to Shah *et al.* paracetamol does not degrade when exposed to acid, base, heat and oxidative stress.<sup>10</sup> In our study, forced degradation analysis was carried out by subjecting paracetamol stock solution to acid (1 N HCl) and alkali (1 N NaOH) hydrolysis, chemical oxidation (3% H<sub>2</sub>O<sub>2</sub>) and dry heat (80°C for 30 minutes). The HCl, NaOH and H<sub>2</sub>O<sub>2</sub> were each mixed in a 2:1 ratio with paracetamol stock solution.

Limb four: Perfalgan® forced degradation study:

The forced degradation study was repeated with Perfalgan® at the same ratios and the samples studied to determine whether significant degradation had occurred.

## 2. Excipient stability testing

<sup>1</sup>H NMR (nuclear magnetic resonance) was used to analyse the changes in the concentration of cysteine and mannitol in Perfalgan® over time. A Bruker 400 <sup>1</sup>H NMR spectrometer locked on to the deuterium signal was used. The Perfalgan® 'stressed' and 'unstressed' solutions were mixed with deuterium oxide (D<sub>2</sub>O) for analysis.

## 3. Bioavailability testing

Paracetamol is believed to have predominantly central nervous system activity. Penetration into a lipid layer is therefore necessary for the effect to take place. Octanol is a hydrophobic organic solvent frequently used for pharmaceutical bioavailability testing. A drug's penetration into the organic layer relative to the hydrophilic layer is measured via the octanol:water partition coefficient. According to the literature, the octanol:water partition coefficient ( $\log P_{ow}$ ) of paracetamol is 0.46–0.49.<sup>13</sup> In this study octanol was added to the paracetamol and Perfalgan® stock solution and UV spectroscopy performed on the aqueous and lipid (or organic) layers to assess the concentration of paracetamol in each. From there the octanol:water partition coefficient was calculated.

## Results

### HPLC results

The paracetamol in Perfalgan® was clearly identified. Figures 2 and 3 show the chromatograms developed. The similarities of the tR identified the paracetamol in the Perfalgan® within the limits of experimental error.

Using the calibration curve generated from analysis of pure paracetamol, the concentration of paracetamol in Perfalgan® was calculated. The calibration curve yielded a straight line with the equation of  $y = 47524x + 8 \times 10^6$ . The  $R^2$  value was 0.98.

The chromatogram of Perfalgan® on exposure to air shows that no degradation of paracetamol occurred after 24 hours (cf. Figure 4).

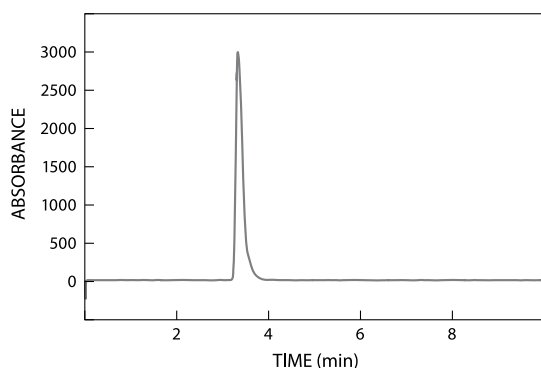


Figure 3: Chromatogram of Perfalgan® 476 µg.ml<sup>-1</sup> at 0 hours.

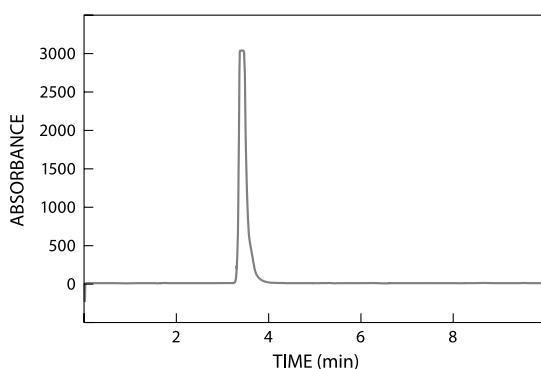


Figure 4: Chromatogram of Perfalgan® 476 µg.ml<sup>-1</sup> at 24 hours.

exposure to heat, acid, base and H<sub>2</sub>O<sub>2</sub>. This was in agreement with extensive literature on paracetamol stability and therefore will not be discussed further. The chromatograms of heated Perfalgan® showed no degradation. On exposure to acid there was visible precipitation within the Perfalgan® sample. The HPLC results confirmed this with < 10% of the paracetamol remaining in solution. Although the HPLC results showed a decrease in the concentration they also showed the same t<sub>R</sub> and that no degradation peaks were present. The same chromatogram was obtained after 24 hours. Due to the precipitation, the calibration curve was not applied as concentrations calculated would be meaningless. Mixing the standard solution of Perfalgan® with base resulted in copious precipitation. While the supernatant could have been analysed by HPLC, judging by the amount of precipitate it was concluded that all the paracetamol had precipitated. Given this assumption and the danger of using high concentrations of base on the HPLC column it was decided not to proceed further with this experiment. Hydrogen peroxide caused splitting of the paracetamol peak (Table 2).

#### Summary of HPLC findings

Quantitative analysis of the paracetamol in Perfalgan® proved difficult using HPLC due to precipitation in the acid-stressed and base-stressed samples and splitting of the peak as in the case of H<sub>2</sub>O<sub>2</sub> exposure. However, quantitative results from the unstressed and heat-stressed samples confirmed the concentration of paracetamol in vial to conform to the manufacturer's specification. No loss was seen with time. Qualitative analysis showed that samples had the same t<sub>R</sub> and no degradation products of paracetamol were seen.

Table 1: Comparison between the area under the peak measured by HPLC (in million units) and the paracetamol concentration (in µg.ml<sup>-1</sup>) in Perfalgan® at 0 and 24 hours

Factor	Standard	
	0 hours	24 hours
Area under peak	32.4	36.4
Concentration	520	600
Standard error	50	50
95% confidence interval	220	230

Table 2: Comparison between the area under the peak measured by HPLC (in million units) and the paracetamol concentration (in µg.ml<sup>-1</sup>) in Perfalgan® on exposure to dry heat

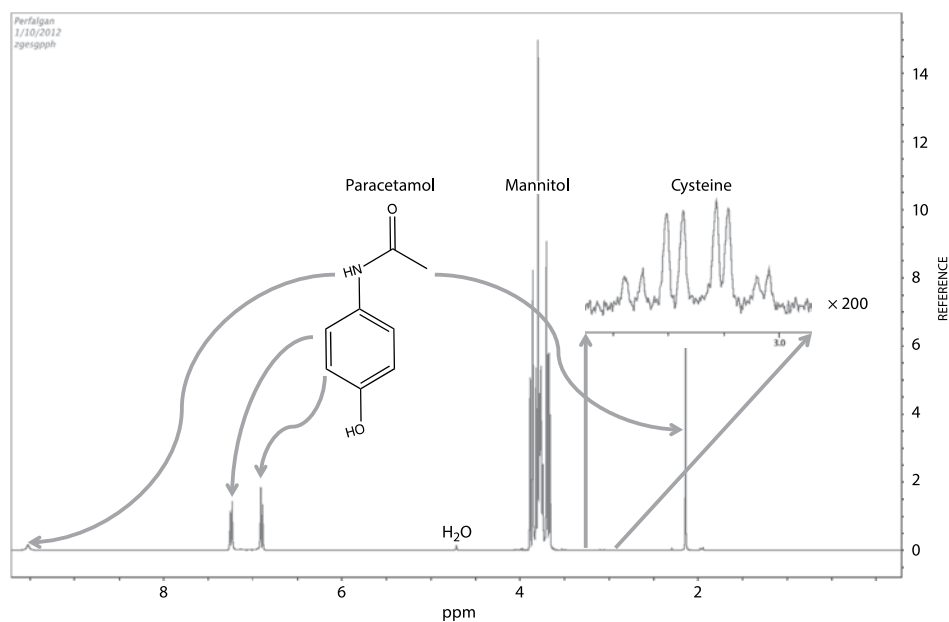
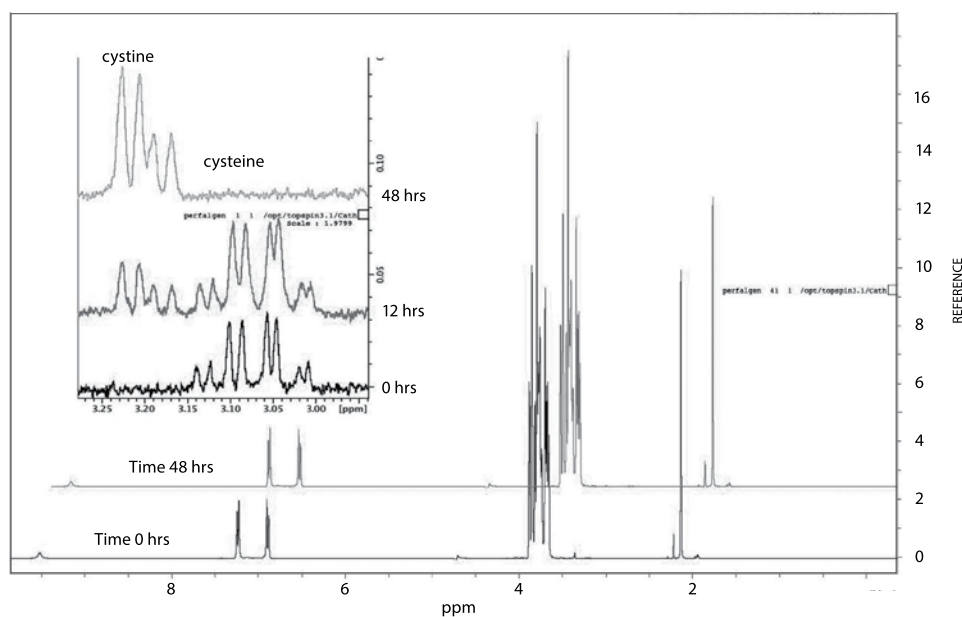
Factor	Heat stressed	
	0 hours	24 hours
Area under peak	33.14	33.05
Concentration	502.7	501.1
Standard error	50	50
95% confidence interval	230	230

Table 1 shows high standard errors due to the standard deviation of the slope. The measured concentration of paracetamol was in keeping with that reported by the manufacturers. Within the experimental error there was no loss of paracetamol over 24 hours.

Chromatograms were generated for paracetamol and Perfalgan® under stressed conditions as per limbs 3 and 4 of the study. The chromatograms of paracetamol remained unchanged after

#### <sup>1</sup>H NMR results

<sup>1</sup>H NMR spectra were created from analysis of 'stressed' and 'unstressed' samples of Perfalgan®. The X-axis shows the proton chemical shift, which is a measure of the magnetic shielding of the nucleus and hence its chemical environment. The Y-axis shows the absorption intensity. The area under the peak is proportional to the number of protons in the compound. Standard tables<sup>14</sup> were used to identify the main constituents in


 Figure 5:  $^1\text{H}$  NMR spectrum of Perfalgan®.

 Figure 6:  $^1\text{H}$  NMR spectrum of Perfalgan® at 0 hours and after 48 hours of exposure to air.

Perfalgan®, namely paracetamol, cysteine and mannitol. In Figures 5 and 6 the cysteine spectrum is shown as an insert at two hundred times magnification as its concentration is much lower than the other two constituents. Where two time periods are shown on the same figure, the spectra are offset slightly for clarity. Using integration of the  $^1\text{H}$  NMR data, it was possible to calculate the concentration of each constituent in Perfalgan® as the concentration of paracetamol is known to be  $10 \text{ mg}\cdot\text{ml}^{-1}$  (cf. Table 3).

The spectra of Perfalgan® did not change significantly over time or on stressing. The only change was that on exposure to air, over time, cysteine oxidised to form cystine. This change occurred more quickly on exposure to heat and hydrogen peroxide. All

cysteine was converted to cystine within 1 hour with addition of hydrogen peroxide, 12 hours with heating and 48 hours in the unstressed sample. There was no change in the paracetamol or mannitol in any samples.

#### UV spectroscopy results

The HPLC instrument used in our study could only look at a single wavelength, which was chosen to be that of paracetamol. It is therefore possible that degradation products absorbing at different wavelengths could have been missed. For this reason ultraviolet spectroscopy was used to assess the samples in the wavelength range 200 to 800 nm. At the same time, since UV can be quantitative, the experiments were also used to check the HPLC quantitation.

Table 3: Comparison of the major three constituents in Perfalgan®

Constituent	Molar ratio derived by <sup>1</sup> H NMR	Molecular weight (g.mol <sup>-1</sup> )	Concentration (mg.ml <sup>-1</sup> )	Concentration (mM)
Paracetamol	1	151.17	10	66.15
Mannitol	1.24	182.17	14.97	82.18
Cysteine	0.004	121.16	0.03	0.25

Note: The concentrations of mannitol and cysteine in Ofirmev® are roughly twice that of Perfalgan®.

Table 4: Comparison of log  $P_{ow}$  of various Perfalgan® samples

	pf:oct 0hr	pf:oct 24hr	pf:oct acid 0hr	pf:oct acid 24hr	pf:oct H <sub>2</sub> O <sub>2</sub>	pf:oct heat
log $P_{ow}$	0.48	0.46	0.36	0.43	0.57	0.56

Notes: Calculations were performed on numbers to three decimal places. This table shows only the first two decimal places.

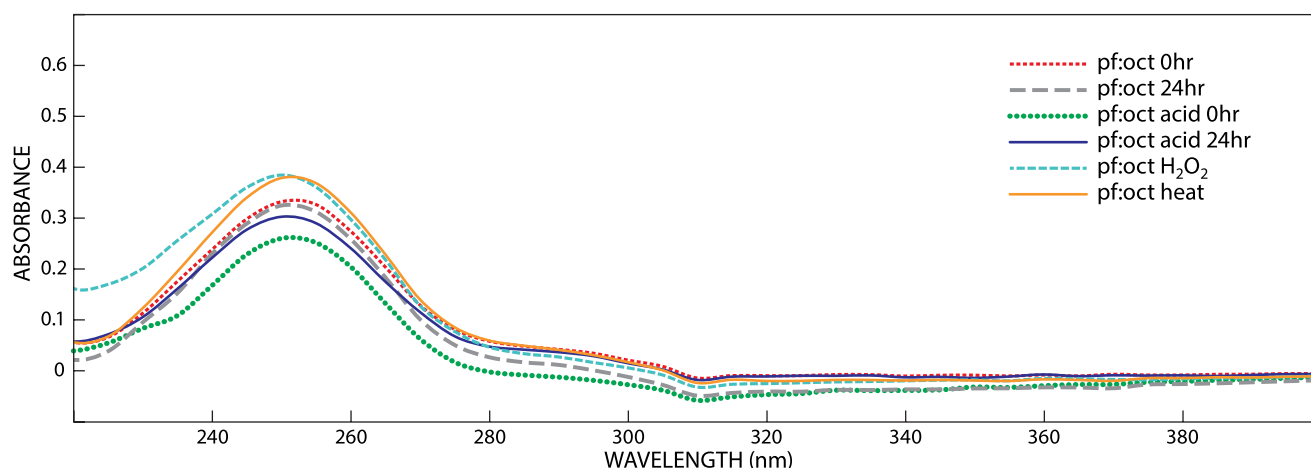


Figure 7: UV spectrum of the organic layer in 50:50 Perfalgan®:octanol.

As with HPLC the equipment was calibrated with altering concentrations of paracetamol at 245 nm. The equation of the straight line was  $y = 0.0424x + 0.0141$ . The  $R^2$  value was 0.94, making it a less precise method than HPLC. The standard error was also greater than the HPLC at 0.02. For this reason HPLC was used as the main method for quantifying paracetamol.

UV spectroscopy was first performed on paracetamol mixed in octanol to create a calibration curve, which yielded a straight line with equation of  $y = 0.2812x - 0.6718$ . The  $R^2$  value is 0.97 making it an accurate calibration curve. UV spectroscopy was then performed on 'stressed' and 'unstressed' Perfalgan® samples mixed with octanol. Since Perfalgan® is formulated in water, the octanol formed a layer above the aqueous layer. Each layer was analysed for paracetamol (cf. Figure 7). (In the key 'pf' represents Perfalgan®.)

Using the paracetamol:octanol calibration curve it was possible to calculate the concentration of paracetamol recovered in each Perfalgan® sample. The concentration in the organic (or octanol) layer was subtracted from the known total concentration of 4.76  $\mu\text{g.ml}^{-1}$  in the stock solution to give the concentration in the aqueous layer. Although measurements of each layer (i.e. organic and aqueous layer) could have been performed it is common practice to measure the concentration of a drug in one layer and calculate the concentration in the other. The ratio of these two values is the octanol:water partition coefficient. The coefficient is often also given as the log of this value. The samples show good agreement with the literature where the partition coefficient (log $P_{ow}$ ) of paracetamol is quoted as 0.46–0.49 (Table 4).<sup>15,16</sup>

### Summary

The concentration of paracetamol penetrating the lipid or aqueous layer remained constant despite stress applied to the Perfalgan® samples over 24 hours. This implies that bioavailability was unaltered.

### Discussion

Each method of analysis showed a well-defined peak for paracetamol. The t<sub>R</sub> using HPLC was in the range of 3.2 to 3.3 minutes, which correlated well with that found in the literature. Although subjected to extreme conditions the paracetamol in Perfalgan® did not degrade.

A variety of methods was used to analyse Perfalgan® in this study. While HPLC was more accurate than UV spectroscopy (with an  $R^2$  value of the calibration curve of 0.98 as opposed to 0.94 and smaller standard error) it was limited by the fact that it analysed paracetamol at only one wavelength, 266 nm.

### HPLC results

The paracetamol in Perfalgan® did not degrade significantly over a 24-hour period on exposure to air. Of the stressed samples, the paracetamol in heated Perfalgan® was unchanged. The Perfalgan® was found to precipitate in base precluding further analysis with HPLC. Filtered samples showed very small peaks at the same retention time due to loss of paracetamol by the filtering process. The precipitation may be the paracetamol alone or contain buffer from the mobile phase. Further studies with different mobile phases would need to be done to elucidate this.



Acid-stressed Perfalgan® samples showed a paracetamol peak at the same tR but with reduced area under the peak. There is little difference between the 0-hour and 24-hour acid samples. Again, this was due to precipitation of the active ingredient when subjected to acid in a methanolic solution. Since the peak is at the same tR and shape, it is unlikely to be due to paracetamol degradation.

Subjecting Perfalgan® and paracetamol stock solution to hydrogen peroxide gave a double peak in the HPLC chromatogram. Two peaks could be due to two different compounds eluting with similar retention times, i.e. one peak is paracetamol and the other is a degradation product. Since this did not occur with UV spectroscopy or NMR, it may be concluded that this is not two peaks but a splitting of the paracetamol peak. Split peaks are known to occur in HPLC because the injected volume or sample concentration is too high. Since the same injection volume and sample concentration were used in all the experiments this is unlikely to be the cause of the split peak. Similarly we can discount a column void or channelling as the reason for the peak splitting. The most likely reason is a polarity difference between the mobile phase and injection solvent. The high concentration of peroxide in the injectate relative to the mobile phase caused the peak to split. It should be mentioned that splitting of the peak occurred originally when pure Perfalgan® was injected, therefore methanol was added to the samples to more closely match the polarities. It was decided not to pursue the cause of the split peaks further as it was not part of the main objectives of the study.

Quantitative analysis of the paracetamol in Perfalgan® proved difficult using HPLC due to precipitation in the acid-stressed and base-stressed samples and splitting of the peak as in the case of H<sub>2</sub>O<sub>2</sub> exposure. However, qualitative analysis showed that samples had the same tR and no degradation products of paracetamol were seen.

#### **<sup>1</sup>H NMR results**

NMR showed Perfalgan® to be stable. The paracetamol peak was unaltered in each sample. Of its excipients only cysteine changed under the various tests performed. On exposure to air the cysteine oxidised to cystine. This process took 48 hours under 'unstressed' conditions, but was much faster under 'stress', i.e. 12 hours on heating and 1 hour on addition of H<sub>2</sub>O<sub>2</sub> respectively. The Perfalgan® package insert lists cysteine as an antioxidant that is added to protect the paracetamol from oxidative stress.

#### **UV spectroscopy results**

UV spectroscopy again showed a constant concentration of paracetamol over time and on exposure to stressors. On calculating the concentration of paracetamol in each sample the values were much higher than expected, presumably due to another species in the vial absorbing at the same wavelength. The method of standard additions should have been used to quantify the paracetamol rather than the calibration curve. Since H<sub>2</sub>O<sub>2</sub> has its own absorbance it was not possible to assess the peroxide-stressed Perfalgan® samples using this method.

#### **Octanol:water partition coefficient**

The concentration of paracetamol in the octanol (or organic layer) remained constant despite stress applied to the samples. LogP<sub>ow</sub> was 0.48 for Perfalgan® at 0 hours and did not change significantly over time and under 'stress'. Although being calculated and not directly measured, this value shows good

agreement with the literature, which quotes the figure between 0.46 and 0.49. The logP<sub>ow</sub> values for H<sub>2</sub>O<sub>2</sub>-treated and heat-treated Perfalgan® were about 20% greater than unstressed. LogP<sub>ow</sub> values of < 1 indicate high solubility, 1–3 moderate solubility and 3–5 low solubility. Within this context it is clear that this increase does not have a significant impact on the drug's solubility.

#### **Conclusions**

In summary, three different assay methods showed the paracetamol in Perfalgan® was stable with regard to its structure, concentration and bioavailability over a 24-hour period and despite changing its environment. It follows that the practice of using a single vial of Perfalgan® multiple times over the course of a day will render a constant concentration of paracetamol, of equal bioavailability at the end of the day relative to a newly opened vial. The practice of using Perfalgan® as a multidose vial is therefore valid from a chemical point of view. Concerns about under-dosing children from a previously opened vial are invalid.

Sterility may be a legitimate barrier to the clinical application of this process and further microbiological testing should be performed before this practice can be fully endorsed.

*Conflict of interest* – There are no conflicts of interest to declare

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