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Stability indicating HPLC method for the estimation of oxycodone and lidocaine in rectal gel

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Abstract

An HPLC method for the quantification of oxycodone and lidocaine in a gel matrix is described. The mobile phase consisted of methanol–water–acetic acid (35:15:1 v/v/v) and was delivered at 1.5 ml/min through a 4.6 × 250 mm Zorbax® SB-C8 column. Oxycodone was detected at 285 nm and lidocaine at 264 nm. Linear calibration curves were obtained for oxycodone in the range of 0.05–1.5% (w/w) and for lidocaine in the range of 0.1–5.0% (w/w). Oxycodone and lidocaine were treated with hydrogen peroxide and the oxidation products were readily separated on the column. The method was applied to assess the stability of a gel containing oxycodone hydrochloride (0.3% w/w) and lidocaine (1.5% w/w). The gel was stored under refrigeration in ready-to-use syringes and under these conditions oxycodone and lidocaine were stable for at least 1 year. The gel is useful in the management of tenesmus in rectal cancer.

Keywords: Oxycodone; Lidocaine; HPLC; Rectal gel

1. Introduction

Oxycodone, a potent opioid, is widely used to manage cancer pain (Poyhia et al., 1993). Lidocaine is a local anaesthetic that can be rectally administered in a gel matrix (Stegman and Stoukides, 1996). At our institution, oxycodone–lidocaine gel is used for the management of tenesmus in rectal and colorectal cancer. We were interested in the stability of oxycodone and lidocaine in the gel matrix. There is a current paucity of data on the chemical stability of oxycodone in pharmaceutical formulations and we developed and validated a method based on HPLC with UV detection. We will report on the stability of oxycodone and lidocaine.

2. Materials and methods

2.1. Materials and instrumentation

Oxycodone hydrochloride was obtained from Macfarlan Smith and lidocaine gel from Delta West (now Pharmacia). The lidocaine gel con-

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tained 20 mg of lidocaine and 1 mg of methyl hydroxybenzoate per gram of gel base, which consisted of propylene glycol hydroethyl cellulose and water. Hydrogel was obtained from Smith and Nephew (Intrasite Gel®) and contained a modified cellulose polymer, propylene glycol and water. Methyl 4-hydroxybenzoate (Aldrich) and a 2% aqueous solution of lidocaine hydrochloride for injection (Xylocaine®, Astra) were used as standards. HPLC-grade methanol (BDH), glacial acetic acid (BDH), sodium dodecyl sulphate (BDH) and Milli-Q water were used for the HPLC solvent. Disposable filtration tubes for centrifugation fitted with a molecular weight cut-off membrane of 30 kDa (Centrifree®) were purchased from Amicon and a 4.6×250 mm reverse phase Zorbax® SB-C8 HPLC column (5 micron) from Hewlett Packard.

A preparative benchtop centrifuge (Megafuge 1.0R, Hereaus) was used for centrifugation of gel samples. The HPLC apparatus (Waters) consisted of a pump (model 510) controlled through an interface (SIMS), an autoinjector (W717) and a photo diode array detector (PDA996). The apparatus was controlled using Millenium32® software (Waters).

2.2. Preparation of the gel

Oxycodone hydrochloride powder (1.05 g) and lidocaine gel (262.5 g) was mixed with hydrogel (86.45 g) by the method of doubling. The gel was packed into 50 ml luer lock syringes attached to a three-way stopcock and transferred into a 10 ml slip lock syringe to the 5 ml mark via the other port of the three-way stopcock. Through this procedure air bubbles were almost completely removed. Syringes were stored in a fridge at 4° for 12 months.

2.3. Stability study

To 20 ml of a 2% (w/w) aqueous solutions of lidocaine hydrochloride (in a second experiment a 2% aqueous solution of oxycodone hydrochloride was used) a 5% solution of sodium hydroxide was added dropwise until a precipitate just persisted. Then 1 ml of a 35% solution of hydrogen peroxide was added and the mixture stirred at ambient temperature. Aliquots of the mixture were removed after certain time intervals, added to an equal volume of 1 N hydrochloric acid and analysed by HPLC.

2.4. Analysis

Samples for calibration were prepared by adding oxycodone hydrochloride or lidocaine hydrochloride to the hydrogel in varying amounts ranging from a final concentration of 0.05–1.5% (w/w) for oxycodone and 0.1–5.0% (w/w) for lidocaine. Approximately, 0.5 ml of the gel was placed into a disposable filtration tube and centrifuged at $2600 \times g$ for 30 min at 10°. The filtrate was transferred into a HPLC sample vial with a small volume insert and analysed within 12 h. Samples were prepared monthly from each batch.

Standards of methyl 4-hydroxybenzoate were prepared in methanol. The solvent for elution was prepared by mixing methanol (350 ml), water (150 ml) and acetic acid (10 ml). Sodium dodecyl sulphate (1.60 g) was added and dissolved by stirring and the solution filtered through a 0.2 micron membrane under vacuum. The solvent was delivered at a rate of 1.5 ml/min and the eluant monitored by UV in a range from 250 to 300 nm. The resolution of the detector was set at 6.0 and the sampling rate was 1 point per s. Chromatograms were extracted from the contour plot at 264 nm for lidocaine and at 285 nm for oxycodone. The areas of the peaks at a retention time of 5.05 min (oxycodone) and of 8.00 min (lidocaine) were integrated. Accuracy expressed as the percent analytical recovery (% A.R.) was assessed by determination of drug concentration in gel samples and analytical standards of oxycodone hydrochloride and lidocaine hydrochloride in water. Precision, expressed as percent coefficient of variation (% C.V.) was calculated from the back-calculated concentrations generated using the regression curves from each calibration curve.

2.5. Statistics

Peak areas for oxycodone and lidocaine were converted into concentrations (% w/w) and plotted as a function of the number of months elapsed since the preparation date of a batch of oxycodone–lidocaine gel. The data for each batch were analysed by linear regression using the program Statistica® 6.0 and the slopes of the fitted lines compared with a slope of zero, which is slope that would be expected if no time-dependent change of the peak area was to occur (null-hypothesis). A t-test was performed on the slope with a two-tailed $\alpha = 0.05$ denoting statistical significance.

3. Results

Three peaks were observed in all chromatograms of the gels (Fig. 1). These were due to the preservative methyl 4-hydroxybenzoate, and the two active ingredients oxycodone and lidocaine. Significant peak fronting of the oxycodone peak was avoided by the relatively high methanol content of the solvent (Brogle et al., 1999). Calibration curves were fitted for oxycodone and lidocaine by linear regression and gave correlation coefficients above 0.998. The C.V. for inter-day analysis was 2.68% for oxycodone and 3.04% for lidocaine. The analytical recoveries were 98.2% for oxycodone and 97.6% for lidocaine.

Six batches of oxycodone–lidocaine gel were prepared over a period of half a year and analysed monthly. The oxycodone and lidocaine content was plotted as a function of time elapsed since the preparation date (Fig. 2). Each batch was analysed by linear regression (fitted lines are not shown). Table 1 depicts the changes in oxycodone and lidocaine content of the gels over a 12-month-period. These changes were calculated using the slopes of the linear regression analyses and tested for statistical significance using a t-test. The resultant P-values indicated whether the calculated changes in oxycodone and lidocaine content over the 12-month-period were statistically significant. In no case was a significant change detected. This was consistent with oxycodone and lidocaine being stable within the detection limits of this method. An inspection of the 95% confidence intervals (not shown) of the fitted curves

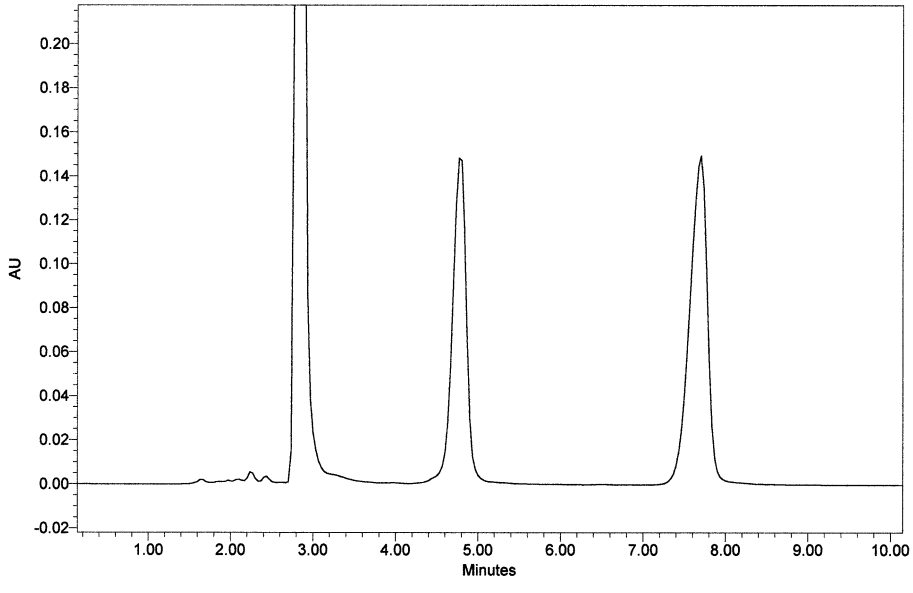

Fig. 1. Chromatogram at 274 nm of a filtrate of oxycodone (0.3% w/w)–lidocaine (1.5% w/w) gel, which had been stored for 12 months. The peaks are in order of increasing retention time: methyl hydroxybenzoate, oxycodone and lidocaine.

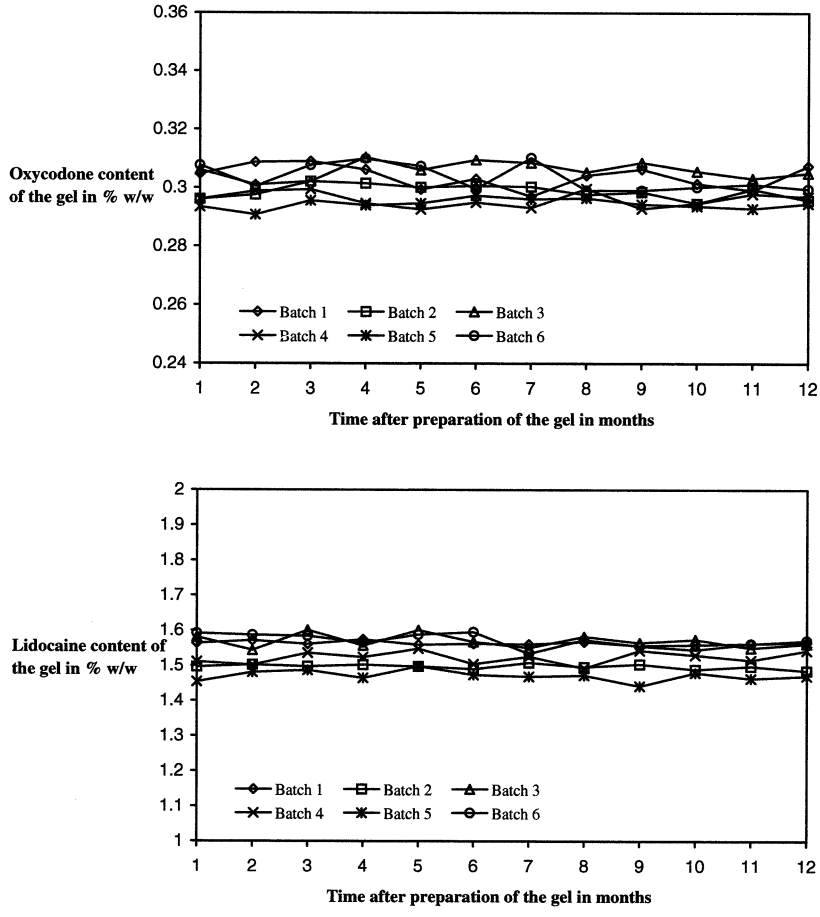

Fig. 2. Oxycodone and lidocaine content of six batches of rectal gel.

Table 1
Calculated relative changes in the oxycodone and lidocaine contents of the six batches of rectal gel over a 12-month-period

		Batch					
		1	2	3	4	5	6
Oxycodone	Change in %	−1.37	−0.86	0.29	−0.29	0.37	−2.75
	P-value	0.47	0.30	0.78	0.76	0.57	0.06
Lidocaine	Change in %	−0.31	−0.53	−0.76	0.79	−0.06	−2.26
	P-value	0.37	0.25	0.55	0.53	0.95	0.06

Changes were calculated using the slopes of the linear regression analysis of the data depicted in Fig. 2 (see text). $P < 0.05$ indicate that a calculated change is statistically significant.

allowed us to estimate that with this method we would have easily detected any decrease in the oxycodone and lidocaine contents exceeding 5% per annum. Overall there was a statistically non-significant trend for a small decrease in the content of oxycodone and lidocaine, in particular for batch 6. This decrease may be a result of the formation of decomposition products from oxy-

codone and lidocaine, however, we were unable to detect any additional peaks in the chromatograms. We investigated whether decomposition products could be formed under harsher conditions and whether they could be detected by HPLC. Aqueous solutions of oxycodone hydrochloride and lidocaine hydrochloride were pronounced stable to prolonged heating and even evaporation of the solvent to dryness. As oxycodone is similar in structure to morphine, one would expect that similar oxidation products can be obtained following treatment with hydrogen peroxide at a pH when oxycodone is at least partially present as the free base. For example, it would be feasible for an oxidation of the nitrogen of oxycodone to occur with a resultant formation of an *N*-oxide and dimerisation to give pseudooxycodone, a product analogous to pseudomorphine. Treatment of oxycodone with hydrogen peroxide resulted indeed in the formation of several oxidation products with shorter retention times than the parent oxycodone peak (Fig. 3). Following prolonged treatment with hydrogen peroxide a single peak remained with a retention time of 4.2 min. The UV spectrum of this peak was very similar to that of oxycodone with a local maximum at 285 nm characteristic of morphine derivatives. Spiking of this sample with oxycodone confirmed that the peak at 4.2 min was due to a derivative of oxycodone. Following the same treatment, lidocaine was completely converted into a product that eluted 40 s before the parent lidocaine peak. These results demonstrate that the method is suitable to separate and detect the products of oxidative decomposition of oxycodone and lidocaine.

4. Discussion

A number of assays have been developed for the analysis of oxycodone in plasma (Kapil et al., 1992; Wright et al., 1998), but little is known about the stability of oxycodone in pharmaceutical preparations. We have developed and validated a simple and efficient HPLC method to quantify the stability of oxycodone and lidocaine in a gel matrix. Sample manipulations were min-

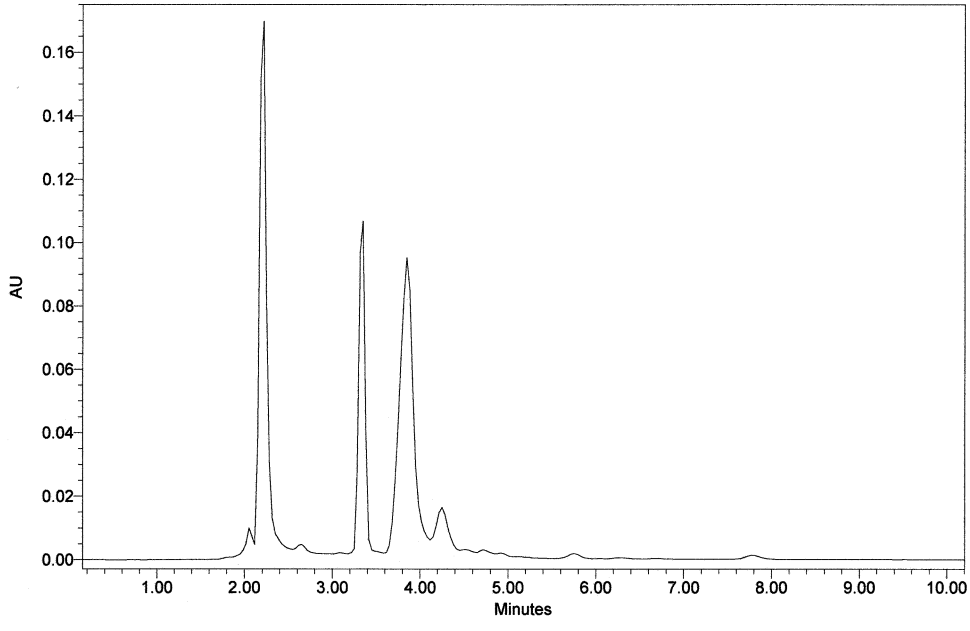

Fig. 3. Chromatogram at 274 nm of the decomposition products of oxycodone solution, which have been obtained by treatment with hydrogen peroxide.

imised and consisted of a simple centrifugation/filtration step of the gel. An internal standard was not required as the method had sufficient precision. The method was sufficiently sensitive to detect a level of degradation of oxycodone or lidocaine of 5% per annum. With this method no degradation of either compound was detected. This result presents useful knowledge for pharmaceutical manufacturing in hospitals where oxycodone–lidocaine rectal gel can be prepared in larger batches and stored under refrigeration for up to 1 year prior to use.

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