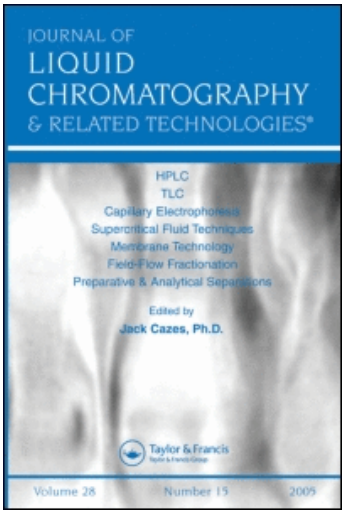

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HPLC-DAD METHOD FOR STUDYING THE STABILITY OF SOLUTIONS CONTAINING MORPHINE, DEXAMETHASONE, HALOPERIDOL, MIDAZOLAM, FAMOTIDINE, METOCLOPRAMIDE, AND DIMENHYDRINATE

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HPLC–DAD METHOD FOR STUDYING THE STABILITY OF SOLUTIONS CONTAINING MORPHINE, DEXAMETHASONE, HALOPERIDOL, MIDAZOLAM, FAMOTIDINE, METOCLOPRAMIDE, AND DIMENHYDRINATE

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ABSTRACT

The objectives of this study were to evaluate both the compatibility and the stability of morphine when mixed with different drugs and to provide recommendations for appropriate conservation conditions. Five drug mixtures used for palliative care were stored in polypropylene syringes at different temperatures (25°C, 4°C) up to 96 h. These mixtures were: 1) Morphine, Dexamethasone, Octreotide; 2) Morphine, Dexamethasone, Haloperidol; 3) Morphine, Octreotide, Haloperidol, Midazolam, Famotidine; 4) Morphine, Haloperidol, Famotidine, Metoclopramide; 5) Octreotide,

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Haloperidol, Famotidine, Metoclopramide, Dimenhydrinate. Drug mixtures were prepared in NaCl 0.9%, in order to obtain a 100 mL final solution containing the maximum daily dose of each component. For the separation and quantification of active ingredients, a fast, precise, accurate, and sensitive method was developed. Drugs were separated using HPLC–DAD (High performance liquid chromatography-diode array detector) with a Zorbax® Eclipse XDB C_{18}) column under elution gradient. Just after preparing the mixture of drugs and then after 4, 8, 12, 24, 48, 72, 96 h, the physical appearance of each solution was observed, and drug concentrations were controlled. Stability was assumed if the loss after 96 h was less than 10% of the initial concentration. Mixture number (2) was incompatible when drugs were mixed. Mixing haloperidol and dexamethasone gave rise to the formation of a white precipitate. Mixture (3) was stable and compatible at 25°C, but incompatible at 4°C due to crystallization of haloperidol. All the other drug mixtures were stable and compatible both at 4°C and 25°C for 96 h.

INTRODUCTION

Many cancer patients suffer from pain or other problems due to the progress of their disease or its treatment. To manage the pain, which leads to suffering and diminishes the patient's quality of life, morphine is frequently used as a potent opioid analgesic (1,2).

Many researchers have studied the stability of morphine solutions under different conditions of conservation (3–5). It has been found that the decomposition of morphine is accelerated in alkaline pH (3) and depends on the presence of oxygen (5). The degradation products of morphine are pseudo-morphine and morphine-*N*-oxide and other minor products (3). Morphine can undergo a dimerization reaction when it is stored without preservatives producing pseudomorphine (4).

However, cancer patients who are in terminal phase need more than one drug for their therapy. Mixing drugs will prevent multiple perfusions. Several studies proposed that the combination of drugs may be more affective than monotherapy and it offers different mechanisms of action and different sites of activity (6–8). Most of the stability studies have been carried out on binary drug mixtures (9–18). The stability of single drugs has also been reported by numerous authors (3–5,19–21). However, few studies have been performed on the stability and the compatibility of drug mixtures, which contain more than two active ingredients (22,23).

HPLC methods for determining the drugs involved in this study have already been reported (3–5,9–23). However, there is no available method that permits a

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simultaneous separation of morphine, dexamethasone, haloperidol, midazolam, famotidine, metoclopramide, dimenhydrinate, and of the preservatives present in the pharmaceutical preparations of these drugs. Vermeire et al. developed methods to separate morphine–midazolam, morphine–haloperidol, and the degradation products of morphine, as well as haloperidol and midazolam (9). However, their methods do not allow the simultaneous separation of all the drugs involved in the present study. Furthermore, in their work, a different method of separation was used for each admixture.

The aim of this study was to set up and validate an analytical method able to separate and quantify the seven drugs under study in order to assess both the compatibility and the stability of morphine when mixed with these drugs, and to provide recommendations for the appropriate conservation conditions. The studied mixtures used for palliative care were studied under the usual conditions of their use. They were stored in polypropylene syringes at different temperatures (25°C and 4°C) over 96 h. These mixtures contained the maximal daily concentration of each drug.

The method of separation had to be able to separate the drugs from the preservatives used in their pharmaceutical preparations: creatinine, benzyl alcohol, methylparaben, propylparaben, and had to be fast enough in order to process the numerous samples required for the conservation study.

EXPERIMENTAL

Materials and Methods

Drug Standards

The drugs were obtained from the pharmaceutical department of the Royal Victoria Hospital (Montreal, QC, Canada). Morphine sulphate – 50 mg mL^{-1} (Morphine HP® injection, Sabex), (Pr Haloperidol) Haloperidol base – 5 mg mL^{-1} (Haloperidol injection USP, Sabex) containing lactic acid to adjust the pH, Dexamethasone phosphate – 4 mg mL^{-1}, (Dexamethasone sodium phosphate injection USP, Sabex) containing creatinine, methylparaben, and propylparaben as preservatives, Dimenhydrinate – 50 mg mL^{-1} (Dimenhydrinate IM injection USP, Sabex) containing benzyl alcohol, Famotidine – 10 mg mL^{-1} (Pepcid® IV, Merck), Midazolam – 5 mg mL^{-1} (Versed®, Roche) containing benzyl alcohol, Metoclopramide hydrochloride – 30 mg mL^{-1} (Chlorhydrate de metoclopramide injection, Sabex), Octreotide Acetate – 100 μg mL^{-1} (Sandostatin®, Novartis).

Other chemicals were: sodium chloride 0.9% – 50 mL (Baxter) and anhydrous theophylline (Sigma) was used as internal standard.

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Chemicals

Chemicals used for preparing the mobile phase were: acetonitrile (HPLC grade, Burdick & Jackson), water (HPLC grade, Baker), potassium dihydrogeno-orthophosphate (BDH). The phosphate buffer ($KHPO_4$ 0.05 mol L^{-1}) was prepared by dissolving 13.609 g of potassium dihydrogeno-orthophosphate into 2.00 L of water HPLC grade. The pH of the solution was adjusted to 4.6 with phosphoric acid. All solvents were filtered before use through a 0.45 μm filter (Gelman Sciences).

Apparatus

The HPLC instrument was a Hewlett Packard® Series 1100 liquid chromatograph equipped with a binary pumping system, a degasser, a compartment for the columns in which the temperature was controlled (23°C), an auto-sampler, and a photodiode array spectrophotometer (HP 1100 Series Diode Array Detector). The control of the instrument, as well as data acquisition and treatment were performed using the ChemStation HP software. The chromatographic separation was carried out on a Zorbax® Eclipse XDB C_{18} (3.5 μm, 4.6 × 75 mm) column.

Drug Mixtures

The various drug mixtures studied were: (M1) Morphine 10.00 mg mL^{-1}, Dexamethasone 0.40 mg mL^{-1}, Octreotide 0.01 mg mL^{-1}. (M2) Morphine 10.00 mg mL^{-1}, Dexamethasone 0.40 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}. (M3) Morphine 10.00 mg mL^{-1}, Octreotide 0.01 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}, Midazolam 1.00 mg mL^{-1}, Famotidine 0.40 mg mL^{-1}. (M4) Morphine 10.00 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}, Famotidine 0.40 mg mL^{-1}, Metoclopramide 0.50 mg mL^{-1}. (M5) Morphine 10.00 mg mL^{-1}, Octreotide 0.01 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}, Famotidine 0.40 mg mL^{-1}, Metoclopramide 0.50 mg mL^{-1}, Dimenhydrinate 5.00 mg mL^{-1}.

Sample Preparation

For preparing all the mixtures, the maximal quantity to be administered per day for each of the admixture constituents was introduced into a 100-mL volumetric flask (from each of the commercial preparations).

Drugs were added, one by one, from the most concentrated to the least concentrated one. The volume was completed to 100 mL with NaCl 0.9%.

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Conservation

Each of the solutions (M1 to M5) was distributed into ten 5-mL polypropylene syringes. Batches of five syringes were placed at different controlled temperatures: Five were placed in the refrigerator at 4°C, and the other five were conserved at 25°C.

After the addition of each component of the mixture, immediately after the preparation of the mixture and then 4, 8, 12, 24, 48, 72, 96 h after sample preparation, the physical appearance of each solution was observed on black and white backgrounds with a magnifier, and the concentrations of morphine, dexamethasone, haloperidol, metoclopramide, midazolam, and dimenhydrinate were determined by HPLC.

Analytical Sample Preparation

For the quantitative analysis, an internal standard (500 μL of an aqueous solution of theophylline – 1 mg mL^{-1}) was added to 200 μL of the analyzed sample (mixture from each syringe) into a 5-mL volumetric flask. The volume was then completed to 5 mL with water. 10 μL of the resulting solution were injected into the chromatographic column. Analyses were performed in duplicate.

Chromatographic Separation

A diode array detector (DAD) was used because it offers more advantages than the conventional UV detector. DAD permits the rapid scanning of the full spectrum of a compound as it emerges from the chromatographic column and it offers the multiwavelength detection option (24). According to the UV spectral characteristics of the analyzed compounds, and in order to maximise the sensitivity of the detection, two wavelengths were used for the detection (285 nm and 250 nm).

Theophylline, morphine, famotidine, dimenhydrinate, metoclopramide, and midazolam were detected at 285 nm. Theophylline, dexamethasone, and haloperidol were detected at 250 nm.

Chromatographic behavior of morphine and other constituents of the therapeutic solutions were studied under different conditions of elution. Morphine has a tertiary amine group with a pK value of 6.13, so between pH = 6 and 10 an increase in retention time for morphine was explained by a loss of proton from this group, and the resulting decrease of the positive charge on the amine group. However, above pH = 9.5 an ionization of the phenolic hydroxy group (pKa = 9.85) occurred, which results in a reduction of the retention of morphine (25).

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The final mobile phase was composed of two elution solvents: A: 100% acetonitrile and B: A phosphate buffer at pH = 4.6 ($KHPO_4$ 0.05 mol L^{-1}). Elutions were carried out using an elution gradient according to the following profile: acetonitrile/phosphate buffer (10/90) between $t = 0.00$ and $t = 0.50$ min, then acetonitrile was increased to 35% until $t = 3.00$ min, then to 40% until $t = 4.50$ min. The flow rate of mobile phase was set at 1.0 mL min^{-1}. Under these conditions, the overall analysis cycle was less than 12 min and allowed the process of 20 samples in 4 h.

RESULTS AND DISCUSSION

Chromatographic Separation

Figure 1 shows a typical chromatogram obtained under the conditions described above with detection at both 285 nm and 250 nm. The separation of all the drugs and preservatives is achieved in less than 8 min.

The values in Table 1 show that the reproducibility of the separation is good because the CV% on the retention time is practically always less than 1%. Considering the short retention time of famotidine (Tr = 1.75 min), the CV% value (2.6%) is still very good.

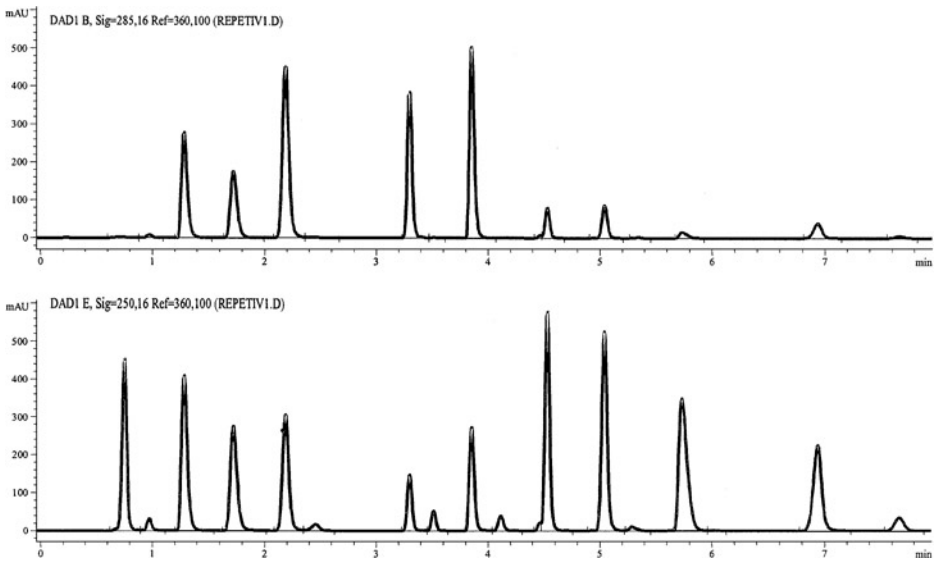

Figure 1. Chromatogram of the optimum conditions. The frame shown above: detection at 285 nm; The frame shown below: detection at 250 nm. To identify the substance that corresponds to each peak see Table 1.

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Table 1. Retention Time (min), Standard Deviation, Coefficient of Variation

Identity[a]	Rt Mean (min) $n = 5$	SD	CV %
CRE	0.76	0.005	0.66
MO	1.31	0.021	1.61
FA	1.75	0.046	2.65
THP	2.22	0.021	0.97
DH1	3.32	0.010	0.30
ME	3.87	0.007	0.17
BAL	4.13	0.007	0.17
DX	4.54	0.006	0.12
MEBEN	5.05	0.007	0.13
DH2	5.30	0.008	0.15
HA	5.75	0.009	0.16
MI	6.96	0.012	0.17
PRBEN	7.68	0.014	0.19

[a]CRE: Creatinine, MO: Morphine, FA: Famotidine, THP: Theophylline (internal standard), DH: Dimenhydrinate, ME: Metoclopramide, BAL: Benzyl alcohol, DX: Dexamethasone, MEBEN: Methlyparaben, HA: Haloperidol, MI: Midazolam, PRBEN: Propylparaben.

Resolution Factor Rs

The resolution factors are shown in Table 2. There was no interference between the analyzed drugs and the various preservatives present in the original pharmaceutical preparations. The resolution factor being always over 1.5 for all successive couples of eluted compounds, all the chromatographic peaks are perfectly separated with return to the baseline.

Asymmetry Factor and Purity Criteria of Chromatographic Peaks

The asymmetry factor and the criteria of purity of the chromatographic peaks, based on the spectral identity of the ultra-violet spectra recorded over each elution peak, were determined for each compound. This is unlike a previous publication (26), which mentioned that the use of an anionic ion pairing agent is required to avoid peak tailing and to achieve a reasonable separation on ODS-silica.

The results obtained under the conditions described previously, showed that all the peaks were symmetrical and pure, so the selectivity of the separation was considered as satisfactory to achieve the objective of the study without the use of any ion pairing agent.

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Table 2. Resolution Factor[a]

Resolution Between Peaks[b]	Rs Mean $n = 5$	SD	CV %
1–2	4.60	0.02	0.52
2–3	5.51	0.13	2.35
3–4	7.51	0.40	5.36
4–5	7.42	0.17	2.26
5–6	3.79	0.10	2.58
6–7	13.39	0.13	1.00
7–8	4.57	0.10	2.21
8–9	7.21	0.06	0.77
9–10	5.13	0.03	0.53
10–11	8.28	0.12	1.46
11–12	10.14	0.09	0.85
12–13	4.00	0.07	1.81
13–14	6.07	0.08	1.39
14–15	3.66	0.05	1.35
15–16	11.83	0.04	0.35
16–17	8.42	0.05	0.62

[a] Average of Resolution Factors: Rs, Standard Deviation: SD, and Coefficient of Variation: CV %

[b] 1–2: Creatinine–P.N.I, 2–3: P.N.I–Morphine, 3–4: Morphine–Famotidine, 4–5: Famotidine–Theophylline, 5–6: Theophylline–P.N.I, 6–7: P.N.I–Dimenhydrinate, 7–8: Dimenhydrinate–P.N.I, 8–9: P.N.I–Metoclopramide, 9–10: Metoclopramide–Benzylalcohol, 10–11: Benzylalcohol–Dexamethasone, 11–12: Dexamethasone–Methylparaben, 12–13: Methylparaben–Dimenhydrinate2, 13–14: Dimenhydrinate2–Haloperidol, 15–15: Haloperidol–P.N.I, 15–16: P.N.I–Midazolam, 16–17: Midazolam–Propylparaben; P.N.I. Peak not identified.

Repeatability of Parameters Used for Quantitative Analysis

The results in Table 3 show that the repeatability of peak area, peak area ratio (analyte/standard), height and peak height ratio was excellent.

Calibration Functions

In the study, each drug was considered stable in solution until it had lost 10% of its initial concentration. So, the calibration functions for all the analyzed compounds were calculated by using 3 concentrations corresponding to the initial

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Table 3. Chromatographic Peaks Area, Area Ratio, Height ($n = 5$)

Identity[a]	Area of Peaks	SD	Area Ratio M/IS[b]	SD	Peak's Mean Height	SD	Height Ratio	SD
CRE	1391.83	32.693	1.14	0.030	444.88	8.912	1.562	0.068
MO	1488.98	5.963	1.21	0.002	395.86	9.876	1.390	0.066
FA	1162.11	3.082	0.95	0.002	298.33	12.746	1.048	0.103
THP	1226.19	5.254	1.00	0.000	284.78	17.891	1.000	0.000
DH1	444.97	1.263	0.36	0.002	148.51	0.679	0.521	0.034
ME	853.52	3.063	0.70	0.005	272.61	1.216	0.184	0.057
BAL	133.91	1.937	0.11	0.002	38.96	0.137	0.957	0.008
DX	1721.90	6.707	1.40	0.008	580.55	1.207	0.137	0.130
MEBEN	1798.42	3.151	1.47	0.006	525.21	0.739	2.039	0.116
DH2	49.34	0.488	0.04	0.000	10.46	0.048	1.221	0.002
HA	1785.80	4.561	1.46	0.009	347.77	0.470	0.005	0.076
MI	1228.47	28.934	1.00	0.020	231.09	4.640	0.811	0.067
PRBEN	202.70	0.341	0.17	0.001	34.47	0.074	0.121	0.008

[a]CRE: Creatinine, MO: Morphine, FA: Famotidine, THP: Theophylline (internal standard), DH: Dimenhydrinate, ME: Metoclopramide, BAL: Benzyl alcohol, DX: Dexamethasone, MEBEN: Methylparaben, HA: Haloperidol, MI: Midazolam, PRBEN: Propylparaben.
[b]IS: Internal Standard.

concentration (at $T = 0$), and this concentration plus and minus 10%. Theophylline was used as the internal standard and it was added to samples at a concentration of 100 μg mL^{-1}.

Each sample was measured in triplicate. Table 4 displays the concentrations of the analytical solutions used for calibration.

The values of the coefficients of regression shown in Table 5 indicate an excellent linearity within the interval between 90–110% of the target concentration for all compounds.

Table 4. Concentrations Used for Calibration

Compound	Initial Concentration (mg mL^{-1})	Concentration After Dilution (μg mL^{-1})	Concentration After Dilution -10% (μg mL^{-1})	Concentration After Dilution $+10\%$ (μg mL^{-1})
Morphine	10.0	400.0	360.0	440.0
Dimenhydrinate	5.0	200.0	180.0	220.0
Haloperidol	0.5	20.0	18.0	22.0
Metoclopramide	0.5	20.0	18.0	22.0
Dexamethasone	0.4	16.0	14.4	17.6

Table 5. Calibration Functions

Product	Function	r^a
Morphine	$0.0011x - 0.0004$	0.9999
Dexamethasone	$0.0283x + 0.0005$	0.9999
Dimenhydrinate	$0.0067x + 0.0027$	0.9998
Haloperidol	$0.0218x - 0.0004$	0.9999
Metoclopramide	$0.0084x + 3.10^{-5}$	0.9989
Famotidine	$6.5999x - 0.0013$	0.9977
Midazolam	$12.575x - 0.0061$	0.9983

[a] r = coefficient of regression.

Results of Stability Studies

Tables 6 and 7 present the results of the measured concentration expressed as the percentage of remaining drug at different times for the various drug mixtures studied under different conditions of temperatures (4°C and 25°C).

In this study, the compatibility and the stability of the maximal daily dose for a patient was examined. There was no interference of the analytes with their degradation products and chromatographic peaks were pure throughout all the study.

Keyi et al. have studied the stability and the compatibility of binary mixtures containing famotidine (17). They mixed famotidine (2 mg mL^{-1}) with dexamethasone (1 mg mL^{-1}), haloperidol (0.2 mg mL^{-1}), metoclopramide (5 mg mL^{-1}), morphine (1 mg mL^{-1}), midazolam (1.5 mg mL^{-1}), and other compounds. They separated the drugs by reverse phase HPLC. The mobile phase was (30 mM sodium orthophosphate adjusted to pH 2.8: acetonitrile) (93:7) with a flow rate of 1 mL min^{-1}. All those binary mixtures were compatible.

In the present study, mixture M4 contains: morphine 10.00 mg mL^{-1}, haloperidol 0.50 mg mL^{-1}, metoclopramide 0.50 mg mL^{-1}, and famotidine 0.40 mg mL^{-1}. Mixture M4 was stable and compatible at both 4°C and 25°C, as shown in Tables 6 and 7. Mixture M3 contains: morphine 10.00 mg mL^{-1}, octreotide 0.01 mg mL^{-1}, haloperidol 0.50 mg mL^{-1}, midazolam 1.00 mg mL^{-1}, and famotidine 0.40 mg mL^{-1}.

Mixture M3 was stable and compatible at 25°C. However, this mixture was incompatible when conserved at 4°C. The formation of a precipitate on the surface of polypropylene syringes was observed after 24 h. The precipitate has a crystalline and transparent aspect. Crystals were of irregular form. They were collected for analysis. The crystals were identified and confirmed as haloperidol by matching the retention time and the UV spectra of both reference haloperidol and the precipitate.

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Table 6. Percentages Remaining of Each Drug in Studied Mixtures at 4°C

Time (h)	0	4	8	12	24	48	72	96
Mixture 1–4 degrees								
Morphine	100.00	99.19	100.25	98.11	100.72	99.59	**	100.89
Dexamethasone	100.00	99.16	100.52	98.49	100.28	99.62	**	100.75
Mixture 3–4 degrees								
Morphine	100.00	100.70	100.28	100.70	100.69	99.80	100.88	101.09
Famotidine	100.00	99.85	100.77	100.58	100.93	100.39	101.08	101.06
Haloperidol	100.00	100.01	100.06	99.99	97.96	86.47	63.99	52.48
Midazolam	100.00	100.96	99.56	100.48	99.84	99.25	101.08	101.31
Mixture 4–4 degrees								
Morphine	100.00	99.54	100.27	100.38	99.71	101.65	99.87	99.44
Famotidine	100.00	99.63	100.44	100.09	99.34	99.91	98.91	98.63
Metoclopramide	100.00	99.66	100.41	100.38	99.78	101.08	99.79	99.62
Haloperidol	100.00	99.53	100.30	100.27	99.62	100.57	96.55	94.60
Mixture 5–4 degrees								
Morphine	100.00	100.46	99.00	99.14	97.95	98.15	99.45	100.80
Famotidine	100.00	100.37	99.26	99.06	99.26	99.49	100.43	101.37
Dimenhydrinate	100.00	100.52	99.25	99.23	98.07	98.36	99.45	100.69
Metoclopramide	100.00	100.46	99.33	99.29	98.37	98.68	99.76	100.98
Haloperidol	100.00	100.57	100.35	99.58	99.75	99.74	100.62	101.29
Mixture 2–4 degrees								
Morphine	INCOMP[a]	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP
Dexamethasone	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP
Haloperidol	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP

** The determination at 72 h has not been performed.

[a] INCOMP: incompatible.

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Table 7. Percentages Remaining of Each Drug in Studied Mixtures at 25°C

Time (h)	0	4	8	12	24	48	72	96
Mixture 1–25 degrees								
Morphine	100.00	100.02	99.85	98.73	101.74	99.77	100.61	100.00
Dexamethasone	100.00	100.13	102.14	100.87	99.80	99.13	100.57	99.45
Mixture 3–25 degrees								
Morphine	100.00	101.33	100.56	101.44	100.56	100.38	100.65	100.31
Famotidine	100.00	102.33	100.74	101.32	99.60	98.38	97.62	96.27
Haloperidol	100.00	100.74	100.32	100.16	100.62	99.70	99.86	100.45
Midazolam	100.00	99.50	98.23	101.09	101.09	100.73	101.00	100.29
Mixture 4–25 degrees								
Morphine	100.00	100.17	99.41	100.17	99.78	101.23	99.78	99.02
Famotidine	100.00	100.29	99.07	99.40	98.93	98.35	96.24	95.60
Metoclopramide	100.00	100.23	99.39	100.06	99.94	100.58	99.61	99.21
Haloperidol	100.00	100.19	99.23	99.99	99.42	100.45	98.86	100.18
Mixture 5–25 degrees								
Morphine	100.00	99.91	99.11	98.08	97.49	97.47	100.55	100.09
Famotidine	100.00	99.94	99.74	97.86	98.90	98.90	100.84	100.04
Dimenhydrinate	100.00	100.02	99.21	98.10	99.37	97.60	100.31	99.83
Metoclopramide	100.00	100.03	99.39	98.13	99.66	97.97	100.83	100.30
Haloperidol	100.00	100.24	100.25	98.53	100.90	99.26	101.70	100.81
Mixture 2–25 degrees								
Morphine	INCOMP[a]	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP
Dexamethasone	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP
Haloperidol	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP	INCOMP

[a]INCOMP: incompatible.

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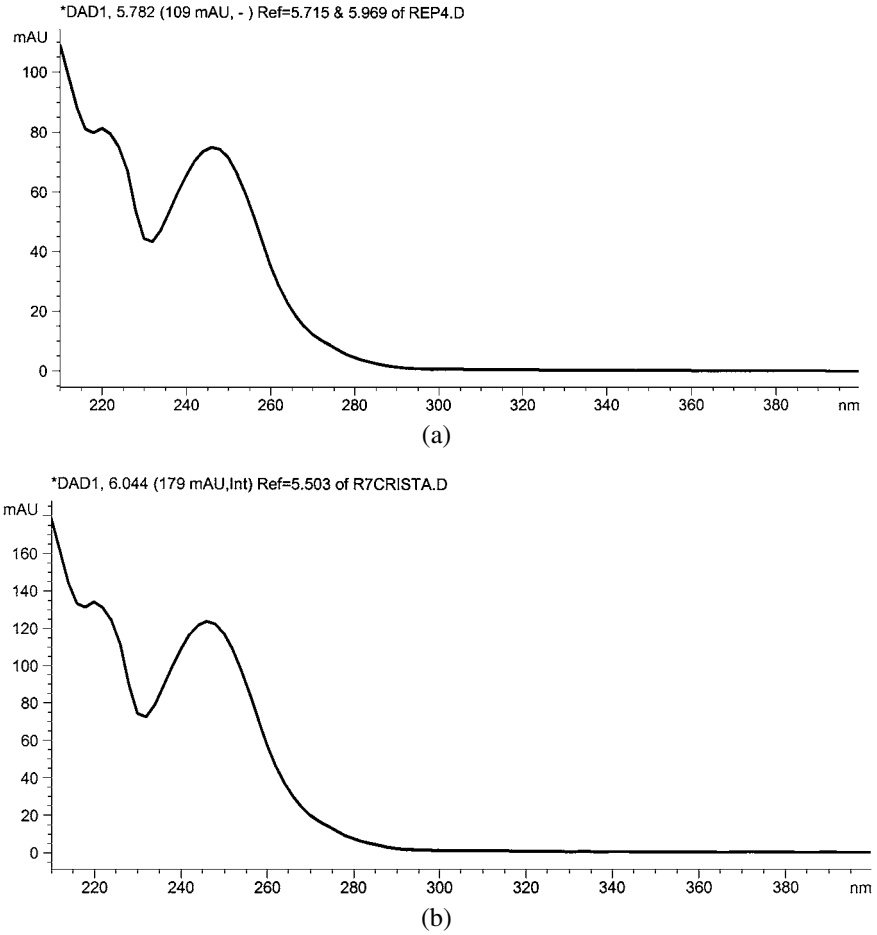

Figure 2. a) UV spectrum of Haloperidol; b) UV spectrum of the crystal.

Figures 2a and b show the UV spectra of the precipitate and haloperidol. Lebelle et al. have studied the stability and compatibility of a similar mixture containing morphine and haloperidol in 0.9% NaCl and 5% dextrose. In that study, the formation of crystals occurred after 24 h of conservation in a glass scintillation vial (20 mL) at ambient temperature. The analysis of those crystals by GC-MS showed that they contained haloperidol, methylparaben, and propylparaben, with no sign of the presence of morphine (27).

In a recent study, Vermeire et al. have optimized the compatibility of a mixture similar to M2 (morphine, haloperidol, and dexamethasone). They found that maximal ratio resulting in effective concentrations of these drugs is (morphine/Decadron® pack/Haldol®) 10/1/1 (v/v/v). However, the concentrations

of dexamethasone-21-sodium phosphate and haloperidol lactate were under therapeutic concentrations. They also found that Decadron® pack is compatible at higher concentrations than Decadron® (23).

Under the conditions of the present study, when these drugs are mixed to prepare the therapeutic mixture M2 at maximal daily dose, the mixture was incompatible. The mixture is incompatible whatever the order of mixing. When morphine was mixed with either haloperidol or dexamethasone, the solutions were compatible. However, an incompatibility occurred when dexamethasone was mixed with haloperidol. Mixing haloperidol and dexamethasone gave rise to the formation of a white fluffy precipitate.

After agitation and settling, a yellow solution can be observed with white particles in suspension, and on the surface of the solution. This precipitate was insoluble in water, soluble in methanol, and soluble in a 0.9% NaCl solution. Octreotide was not analyzed; it was under the limit of detection. All the other mixtures were stable and compatible at 4°C and 25°C until 96 h.

CONCLUSIONS

The method described in this study is a fast, reproducible, and robust method. It allows the separation of morphine, dexamethasone, haloperidol, midazolam, famotidine, metoclopramide, dimenhydrinate, and the preservatives present in their pharmaceutical preparations, and to quantify these drugs. This study is the only one that has checked the compatibility and the stability of maximal daily dose of drug mixtures for palliative care.

Our results show that the mixtures (M1) Morphine 10.00 mg mL^{-1}, Dexamethasone 0.40 mg mL^{-1}, Octreotide 0.01 mg mL^{-1}; (M4) Morphine 10.00 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}, Famotidine 0.40 mg mL^{-1}, Metoclopramide 0.50 mg mL^{-1}; and (M5) Morphine 10.00 mg mL^{-1}, Octreotide 0.01 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}, Famotidine 0.40 mg mL^{-1}, Metoclopramide 0.50 mg mL^{-1}, Dimenhydrinate 5.00 mg mL^{-1}, are stable for 96 h at 25°C and at 4°C. Mixture (M3) Morphine 10.00 mg mL^{-1}, Octreotide 0.01 mg mL^{-1}, Haloperidol 0.50 mg mL^{-1}, Midazolam 1.00 mg mL^{-1}, Famotidine 0.40 mg mL^{-1} is stable at 25°C; nevertheless, M3 was incompatible after 24 h when stored at 4°C. Mixture (M2) Morphine 10.00 mg mL^{-1}, Dexamethasone 0.40 mg mL^{-1}, and Haloperidol 0.50 mg mL^{-1} was incompatible at any temperature.

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