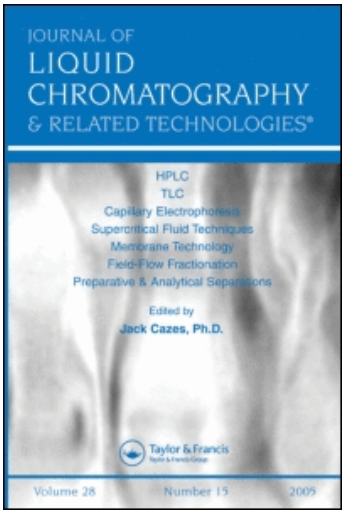

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HPLC-DAD Methods for Studying the Stability of Solutions Containing Hydromorphone, Ketorolac, Haloperidol, Midazolam, Famotidine, Metoclopramide, Dimenhydrinate, and Scopolamine

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HPLC-DAD Methods for Studying the Stability of Solutions Containing Hydromorphone, Ketorolac, Haloperidol, Midazolam, Famotidine, Metoclopramide, Dimenhydrinate, and Scopolamine

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ABSTRACT

The objectives of this study were to evaluate both the compatibility and the stability of hydromorphone when mixed with different drugs and to provide recommendations for appropriate conservation conditions. Four drug mixtures used for palliative care were stored in polypropylene syringes at different temperatures (25°C and 4°C) up to 96 hours. These mixtures were: M1: hydromorphone 10.00 mg mL^{-1}, midazolam 1.00 mg mL^{-1}, famotidine 0.40 mg mL^{-1}; M2: hydromorphone 10.00 mg mL^{-1}, metoclopramide 0.50 mg mL^{-1}, haloperidol 0.50 mg mL^{-1}; M3: hydromorphone

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10.00 mg mL^{-1}, ketorolac 1.50 mg mL^{-1}, metoclopramide 0.50 mg mL^{-1}, famotidine 0.40 mg mL^{-1}; and M4: hydromorphone 10.00 mg mL^{-1}, dimenhydrinate 5.00 mg mL^{-1}, haloperidol 0.50 mg mL^{-1}, famotidine 0.40 mg mL^{-1}, scopolamine 0.04 mg mL^{-1}. 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 fast, precise, accurate, and sensitive methods were developed. Drugs were separated using a high performance liquid chromatography-diode array detector (HPLC-DAD) with a Zorbax® Eclipse XDB C_{18} column under gradient elution. Just after preparing the mixture of drugs and then after 4, 8, 12, 24, 48, 72, and 96 hours, the physical appearance of each solution was observed and drug concentrations were controlled. Stability was assumed if the loss after 96 hours was less than 10% of the initial concentration.

Key Words: HPLC-DAD; Hydromorphone; Ketorolac; Haloperidol; Midazolan; Famotidine; Metoclopramide; Dimenhydrinate; Scopolamine.

INTRODUCTION

Many cancer patients suffer from pain or other problems such as nausea and vomiting (emesis) due to the progress of their disease or to the toxicity of its treatment.[1,2] To manage the pain, morphine is frequently used as a potent opioid analgesic and hydromorphone is used for the same purpose, but for intense pain.[3]

Morphine and hydromorphone have similar structures. The difference between them is the presence of a double bond on the morphine at position 7-8, which is saturated in the hydromorphone molecule. For that reason, hydromorphone is more hydrophilic than morphine, which makes hydromorphone more powerful than morphine. The main advantage of hydromorphone is that it is four times as potent as morphine, allowing for smaller injection or infusion volumes in patients who require opioids to be administrated parenterally.[4]

Subcutaneous infusion is one of the best routes for drug administration in palliative care.[2] Therefore, mixing drugs will avoid multiple perfusions. Several studies done on nausea and vomiting propose that the combination antiemetic regiments may be more effective than monotherapy.[1–5] Several studies have been carried out on the drugs that are studied in this work. The stability of single drugs has been carried on hydromorphone,[6] midazolam,[6] haloperidol,[7] metoclopramide.[8–11] However, few studies have been performed on the stability and the compatibility of drug mixtures, which contain two drugs[10] or more.[12]

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HPLC methods of the drugs involved in this study have been reported,[6–12] but there is no available method that permits a simultaneous separation of the followed drug mixtures: M1: hydromorphone 10.00 mg mL^{-1}, midazolam 1.00 mg mL^{-1}, famotidine 0.40 mg mL^{-1}; M2: hydromorphone 10.00 mg mL^{-1}, metoclopramide 0.50 mg mL^{-1}, haloperidol 0.50 mg mL^{-1}; M3: hydromorphone 10.00 mg mL^{-1}, ketorolac 1.50 mg mL^{-1}, metoclopramide 0.50 mg mL^{-1}, famotidine 0.40 mg mL^{-1}; M4: hydromorphone 10.00 mg mL^{-1}, dimenhydrinate 5.00 mg mL^{-1}, haloperidol 0.50 mg mL^{-1}, famotidine 0.40 mg mL^{-1}, scopolamine 0.04 mg mL^{-1}.

The aim of this study was to set up and validate analytical methods capable of separating and quantifying each of the previous mixtures in order to assess both the compatibility and the stability of hydromorphone when mixed with other drugs and to provide recommendations for the appropriate conservation conditions. Those mixtures, which are used for palliative care, were studied under the conditions in which they are used in Royal Victoria Hospital. They were stored in polypropylene syringes at different temperatures (25°C and 4°C) over 96 hours. These mixtures contain the maximal daily dose of each drug. The methods of separation had to be able to separate the drugs from the preservatives used in some of their pharmaceutical preparations like benzyl alcohol. The methods had to be fast in order to process the numerous samples required for the conservation study. For the study, we prepared therapeutic solutions by mixing the compounds in the decreasing order of their maximal daily dose as shown in Table 1.

Table 1. The order of drug mixing, the maximal daily dose for each drug, and its final concentration in the therapeutic solution.

Order[a]	Molecule	Maximal daily dose (mg day^{-1})	Final concentration (mg mL^{-1})
1	Dihydromorphone	1,000.00	10.00
2	Dimenhydrinate	500.00	5.00
3	Ketorolac	150.00	1.50
4	Midazolam	100.00	1.00
5	Haloperidol	50.00	0.50
6	Metoclopramide	50.00	0.50
7	Famotidine	40.00	0.4
8	Scopolamine	4.00	0.04

[a]The order of mixing.

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EXPERIMENTAL

Materials

Drug Standards

The drugs were obtained from the pharmaceutical service of the Royal Victoria Hospital (Montreal—QC, Canada). Hydromorphone hydrochloride—50 mg mL^{-1} (hydromorphone XP® Injection, Sabex), (Pr haloperidol) haloperidol base—5 mg mL^{-1} (haloperidol injection USP, Sabex) contains lactic acid to adjust the pH, 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), kétorolac tromethamine—30 mg mL^{-1} (Toradol®, Roche) contains 10% (w/v) alcohol USP, scopolamine hydrobromide—0.4 mg mL^{-1} (scopolamine hydrobromide injection USP, Abbott).

Other chemicals: sodium chloride 0.9%—50 mL (Baxter), anhydrous theophylline (Sigma) used as internal standard.

Chemicals

Chemicals used for preparing the mobile phase were: acetonitrile (HPLC grade, Burdick & Jackson), water HPLC grade (J.T. Baker), potassium dihydrogeno-orthophosphate (BDH). The phosphate buffer (KH_2PO_4, 0.05 mol L^{-1}) was prepared by dissolving 13,609 g of potassium dihydrogeno-orthophosphate in 1.8 L of water HPLC grade in a 2.00 L volumetric flask. The pH of the solution was adjusted to 4,6 with phosphoric acid and the volume was completed to 2.00 L by adding water HPLC grade. All solvents were filtered before use with a 0.45 μm filter (Gelman Sciences).

Apparatus

The HPLC instrument used 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 DAD). 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.

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Methods

Sample Preparation

For the preparation of all the mixtures, the maximal quantity to be administered per day of 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 in the decreasing order of their final concentrations. The volume was completed to 100 mL with NaCl 0.9%.

Conservation

Each of the solutions (M1–M4) 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, and 96 hours after sample preparation, the physical appearance of each solution was observed on black and white backgrounds with a magnifier and the concentrations of hydromorphone, dimenhydrinate, metoclopramide, midazolam, haloperidol, and famotidine were determined by HPLC.

Analytical Sample Preparation

For the quantitative analysis, an internal standard (500 μL of an aqueous solution of theophylline 1.00 mg mL^{-1}) was added to 200 μL of the analyzed sample (mixture from syringes) into a 5-mL volumetric flask. The volume was then completed to 5 mL. Then, 10 μL of the resulting solution were injected into the chromatographic column. Analyses were performed in duplicate.

Chromatographic Separation

A DAD was used because it offers more advantages than the conventional UV detector. Diode array detector permits the rapid scanning of the full spectrum of a compound as it emerges from the chromatographic column and it offers the multi-wavelength detection option.[13] According to the UV spectral characteristics of the analyzed compounds and in order to maximize the sensitivity of the detection, we chose different wavelengths for each mixture. Table 2 shows the wavelength used for each product.

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Table 2. Wavelengths of detection (nm).

Products	M1	M2	M3	M4
DHMO	281	285	281	285
DH				285
ME		285	271	
KE			318	
HA		250		250
MI	219			
FA	267		267	270
SCO				Non analyzed

We used three wavelengths to detect the active products in mixture M1: 281 nm for hydromorphone, 219 nm for midazolam, 267 nm for famotidine, and 271 nm for theophylline, as it is shown in Fig. 1.

The detection in the mixtures M2 was performed using two wavelengths: haloperidol and theophylline were detected at 250 nm; hydromorphone, metoclopramide, and theophylline were detected at 285 nm, as it is shown in Fig. 2.

The detection in the mixtures M3 was performed using the maximum wavelength for each compound: hydromorphone 281 nm, metoclopramide 285 nm, ketorolac 318 nm, famotidine 267 nm, and 271 nm for theophylline. Figure 3 shows a typical chromatogram obtained under the conditions described above with detection at both 271 and 318 nm. The separation of all the drugs and preservatives is achieved in less than 8 min.

For the mixture M4 we used three wavelengths: 285 nm for hydromorphone, dimenhydrinate; 250 nm for haloperidol and 270 nm for famotidine. Figure 4 shows a typical chromatogram obtained under the conditions described above with detection at both 250 and 285 nm.

The analysis of Mixtures 2 and 4 have been performed first, then we optimized the detection for the other two mixtures.

Separation of Hydromorphone and Famotidine

Hydromorphone and famotidine had close retention times. We tried several conditions of elution to separate those two components using 0.05 M KH_2PO_4/acetonitrile as a mobile phase.

Hydromorphone elutes before famotidine and the separation was achieved at 5% of acetonitrile with an isocratic elution and a flow rate of 1.00 mL min^{-1}. The quality of separation diminished at higher percentages

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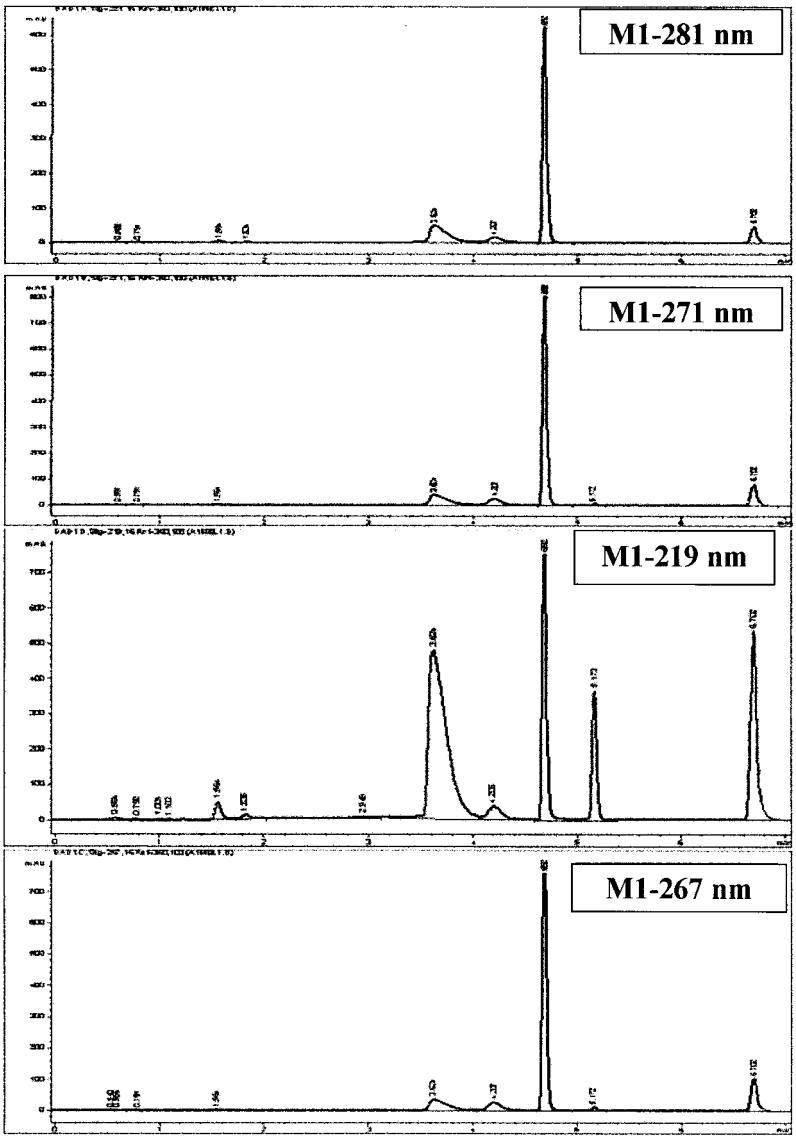

Figure 1. Chromatogram of the mixture M1 at 219, 267, 271, and 281 nm.

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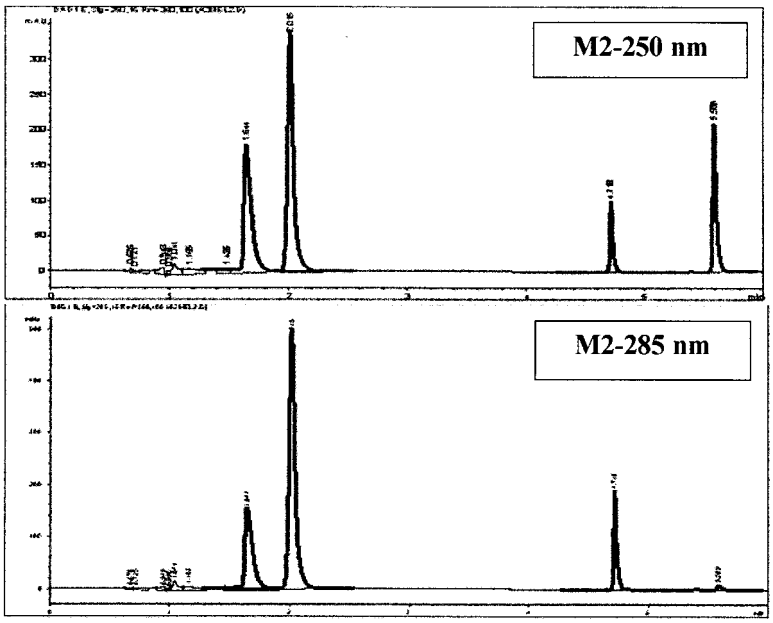

Figure 2. Chromatogram of the mixture M2 at 250 and 285 nm.

of acetonitrile (6%), the retention time of famotidine became closer to the retention time of haloperidol as it is shown in Fig. 5.

The famotidine elutes before hydromorphone, when the percentage of acetonitrile is increased to 10%, as it is shown in Fig. 6. Between 12% and 14% of acetonitrile, the resolution reached its maximum value, but without a complete return to the base line.

The best separation between haloperidol and famotidine was performed using an isocratic separation with 5% of acetonitrile and 95% of phosphate buffer (0.05 M KH_2PO_4) adjusted at (pH 4.6) and the flow rate of the mobile phase was set at 1.00 mL min^{-1}. These conditions are convenient for the mixtures M3 and M4. After the elution of hydromorphone and famotidine, the percentage of acetonitrile was increased to separate the other constituents. For the mixture M1, the flow rate was increased to 1.25 mL min^{-1} to achieve a faster time of analysis.

Separation of the Mixtures M1, M2, M3, and M4

The final mobile phase was composed of two elution solvents: A: 100% acetonitrile and B: a phosphate buffer at pH = 4.6 (KH_2PO_4, 0.05 mol L^{-1}).

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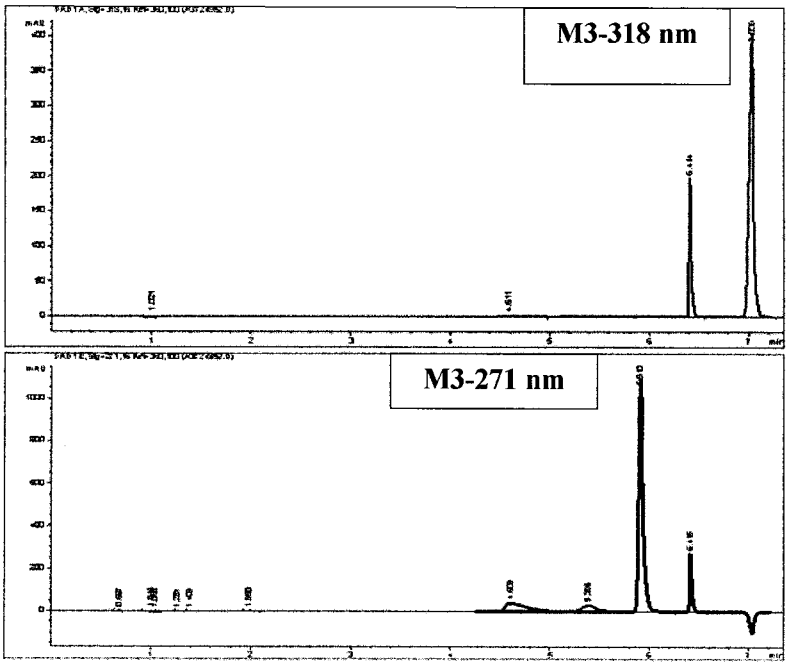

Figure 3. Chromatogram of the mixture M3 at 271 and 318 nm.

Elutions were carried out using an elution gradient according to the following profile: For the mixture M1: acetonitrile/phosphate buffer (5/95) between $t = 0.00$ and $t = .00$ min, then acetonitrile was increased to 35% until $t = 3.50$ min then to 43% until $t = 5.00$ min. The flow rate of mobile phase was set at 1.250 mL min^{-1}.

For the mixture M2: acetonitrile/phosphate buffer (10/90) between $t = 0.00$ and $t = 2.00$ min, then acetonitrile was increased to 50% until $t = 4.00$ min. The flow rate of mobile phase was set at 1.000 mL min^{-1}. Under these conditions the overall analysis cycle was less than 12 min and allowed to process 20 samples in four hours.

For the mixture M3: acetonitrile/phosphate buffer (5/95) between $t = 0.00$ and $t = 3.50$ min, then acetonitrile was increased to 14% until $t = 4.20$ min then to 43% until $t = 4.70$ min. The flow rate of mobile phase was set at 1.000 mL min^{-1}.

For the mixture M4: acetonitrile/phosphate buffer (5/95) between $t = 0.00$ and $t = 3.50$ min, then acetonitrile was increased to 50% until $t = 6.00$ min. The flow rate of mobile phase was set at 1.000 mL min^{-1}.

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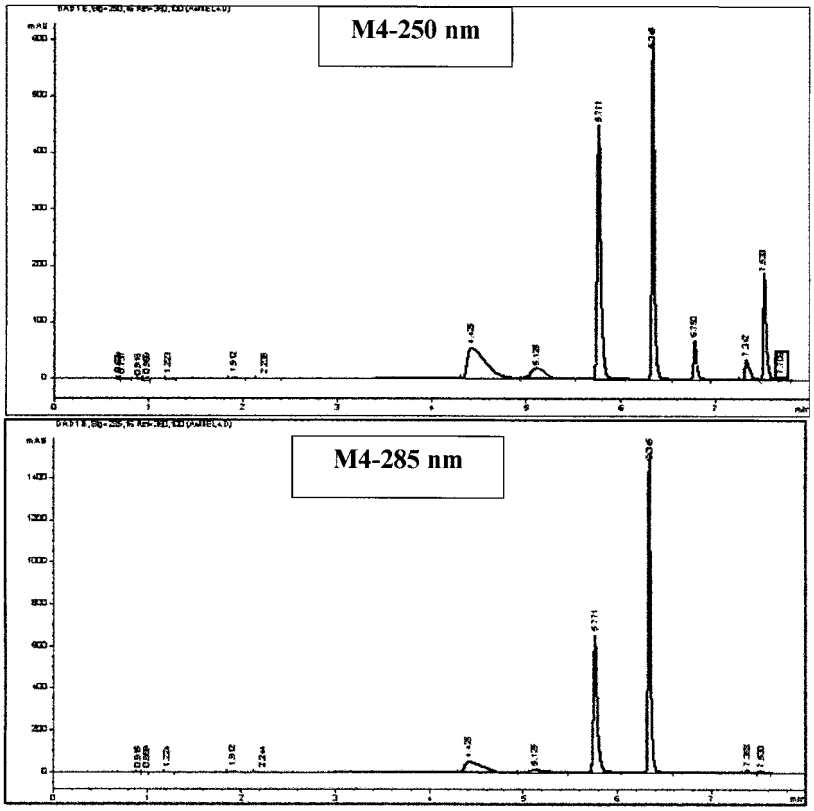

Figure 4. Chromatogram of mixture M4 at 250 and 285 nm.

Under these conditions, the method had an analysis cycle of less than 12 min and allowed processing 20 samples in four hours.

RESULTS AND DISCUSSION

Chromatographic Separation

Figures 1–4 show typical chromatograms obtained under the conditions described above for all the mixtures. The overall separation of the drugs and preservatives is achieved in less than 8 min. The values in Table 3 show that

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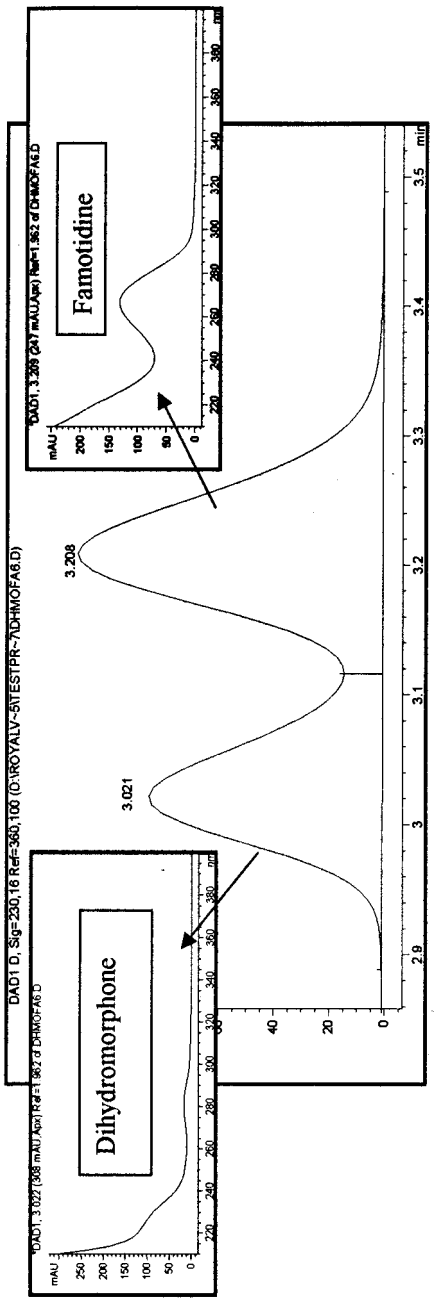

Figure 5. Separation of famotidine and hydromorphone using an isocratic elution 6 : 94 acetonitrile : phosphate buffer (KH_2PO_4, 0.05 M) and the UV spectra of each compound.

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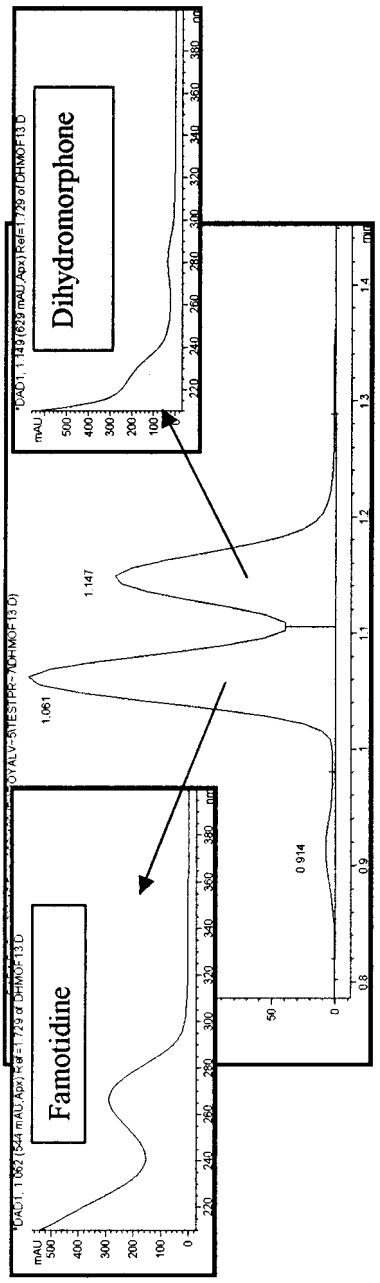

Figure 6. Separation of famotidine and hydromorphone using an isocratic elution 13 : 87 acetonitrile : phosphate buffer (KH_2PO_4, 0.05 M) and the UV spectra of each compound.

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Table 3. Retention time (min), standard deviation, coefficient of variation for the mixtures M1, M2, M3, and M4.

Identity	Rt Mean ($n = 5$)	SD	CV%
Mixture M1			
#1	1.58	0.0077	0.49
DHMO	3.68	0.0060	0.16
FA	4.28	0.0047	0.11
THP	4.70	0.0016	0.03
#2	5.17	0.0016	0.03
MI	6.70	0.0023	0.03
Mixture M2			
DHMO	1.65	0.0028	0.17
THP	2.02	0.0019	0.09
ME	4.72	0.0005	0.01
HA	5.59	0.0016	0.03
Mixture M3			
DHMO	4.43	0.003	0.06
FA	5.14	0.005	0.09
THP	5.85	0.002	0.03
ME	6.41	0.001	0.01
KE	7.02	0.001	0.01
Mixture M4			
DHMO	4.44	0.011	0.24
FA	5.14	0.016	0.30
THP	5.78	0.004	0.06
DH	6.35	0.002	0.04
#	6.79	0.002	0.03
#	7.35	0.004	0.05
#	7.39	0.004	0.05
HA	7.54	0.004	0.05

Note: Rt, retention time; SD, standard deviation; CV%, coefficient of variation; DHMO, dihydromorphone; FA, famotidine; MI, midazolam; ME, metoclopramide; HA, haloperidol; KE, ketorolac; DH, dimenhydrinate; THP, theophylline (internal standard).

the reproducibility of the separation is good because the CV% on the retention time is practically always less than 0.5%.

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. There was no interference between the analyzed drugs

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and the various preservatives present in the original pharmaceutical preparations. The factor of asymmetry and the criteria of purity of the chromatographic peaks, based on the spectral identity of the ultra-violet spectra recorded all over each elution peak, was determined for each compound.

Repeatability of Parameters used for Quantitative Analysis

The results in Table 4 show that the repeatability of area and area ratio, were excellent.

Calibration Functions

In the study, each drug was considered as 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 three concentrations corresponding to the initial 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. Each sample was measured three times. Table 5 displays the concentrations of the analytical solutions used for calibration.

The values of the coefficients of regression indicate an excellent linearity in the interval between 90% and 110% of the target concentration for all compounds, as it is shown in Table 6.

Results of Stability Studies

Tables 7 and 8 present the results of the measured concentrations 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.

In our experiment, the mixtures M1, M3, and M4 contained famotidine, which required a special separation.

The mixture M2 was stable and compatible for 96 hours at 25°C. However, this mixture was incompatible when conserved at 4°C. An increased formation of precipitate on the surface of polypropylene syringes was observed after 12 hours. The precipitate has a crystalline form and was

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Table 4. Chromatographic peaks area, area ratio for the mixtures M1, M2, M3, and M4 ($n = 5$).

Identity	Area of peaks	SD	CV%	Area ratio M/IS	SD	CV%
Mixture M1						
#1	10.79	0.165	1.53	0.0096	0.00015	1.56
DHMO	396.88	0.266	0.07	0.3529	0.00029	0.08
FA	262.12	0.413	0.16	0.2010	0.00044	0.22
THP	1124.77	0.791	0.07	1.0000	0.0000	0.00
#2	43.25	0.394	0.91	0.0384	0.00035	0.91
MI	377.45	0.366	0.10	0.3356	0.00013	0.04
Mixture M2						
DHMO	882.23	13.1	1.49	0.707	0.0098	1.38
THP	1247.19	1.5	0.12	1.000	0.0000	0.00
ME	175.67	0.3	0.17	0.141	0.0001	0.06
HA	434.86	0.7	0.16	0.349	0.0004	0.10
Mixture M3						
DHMO	919.2	1.09	0.12	0.8790	0.0008	0.09
FA	163.9	0.41	0.25	0.1567	0.0004	0.23
THP	1045.7	0.43	0.04	1.0000	0.0000	0.00
ME	189.7	0.16	0.08	0.1814	0.0001	0.04
KE	32.5	0.23	0.71	0.0311	0.0002	0.74
Mixture M4						
DHMO	510.98	0.47	0.09	0.1610	0.000072	0.04
FA	292.11	0.47	0.16	0.0920	0.000214	0.23
THP	3173.98	3.02	0.10	1.0000	0.000000	0.00
DH	1968.39	2.78	0.14	0.6202	0.001080	0.17
HA	82.49	1.63	1.98	0.0260	0.000495	1.91

Note: Rt, retention time; SD, standard deviation; CV%, coefficient of variation; IS, internal standard; M, analyte; #1, peak solvent; #2, conservator; DHMO, dihydromorphone; FA, famotidine; MI, midazolam; ME, metoclopramide; HA, haloperidol; KE, ketorolac; DH, dimenhydrinate; THP, theophylline (internal standard).

transparent with the size of salts table grain and irregular form. They were collected for analysis. We identified the precipitate by matching the retention time and the UV spectra of both haloperidol and the precipitate. Figure 7 shows the UV spectrums of the precipitate and haloperidol.

M4 was stable and compatible during 12 hours. Then, M4 was incompatible at both 4°C and 25°C. A white precipitate appears after 12 hours on the wall of the polypropylene syringe. The formation of precipitate is coupled with a diminution of the quantity of dimenhydrinate, which decreased below the

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Table 5. Concentrations used for calibration.

Compound	Initial concentration ($mg\,mL^{-1}$)	Concentration after dilution ($\mu g\,mL^{-1}$)	Concentration after dilution -10% ($\mu g\,mL^{-1}$)	Concentration after dilution $+10\%$ ($\mu g\,mL^{-1}$)
Hydromorphone	10.0	400.0	360.0	440.0
Dimenhydrinate	5.00	200.00	180	220.00
Ketorolac	1.50	60.00	54.00	66.00
Midazolam	1.00	200.0	180.0	220.0
Metoclopramide	0.50	20.0	18.0	22.0
Haloperidol	0.50	20.0	18.0	22.0
Famotidine	0.40	16.00	14.40	17.60

Table 6. Calibration functions for the mixture M1, M2, M3, and M4.

Product	Function	R
Mixture M1		
Hydromorphone	$0.0012x - 0.0076$	0.9985
Famotidine	$0.0109x + 0.0151$	0.9991
Midazolam	$0.0400x + 0.0339$	0.9998
Mixture M2		
Hydromorphone	$0.0016x - 0.031$	0.9933
Metoclopramide	$0.0151x + 0.0031$	0.9998
Haloperidol	$0.0084x + 0.0056$	0.9979
Mixture M3		
Hydromorphone	$0.0009x - 0.0049$	0.9999
Ketorolac	$0.0149x + 0.0008$	0.9999
Metoclopramide	$0.0058x + 0.0063$	0.9999
Famotidine	$0.0097x - 0.0033$	0.9968
Mixture M4		
Hydromorphone	$0.0006x - 0.0007$	0.9996
Dimenhydrinate	$0.0112x + 0.0107$	0.9993
Haloperidol	$0.0250x + 0.0090$	0.9979
Famotidine	$0.0086x - 0.0097$	0.9940

Note: R, coefficient of regression.

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Table 7. Percentages remaining of each drug in studied mixtures at 25°C.

Time (hours)	0	4	8	12	24	48	72	96
Mixture M1								
Hydromorphone	100.00	101.23[a]		99.91	100.30	101.79	101.14	99.94
Famotidine	100.00	99.67[a]		99.54	100.61	97.57	99.70	97.78
Midazolam	100.00	100.23[a]		99.91	100.30	101.79	101.14	99.94
Mixture M2								
Hydromorphone	100.00	99.63	99.93	99.83	100.44	100.85	100.83	101.76
Metoclopramide	100.00	100.56	100.00	99.98	100.17	100.66	100.48	101.50
Haloperidol	100.00	100.19	99.63	99.60	99.99	100.28	100.37	101.41
Mixture M3								
Hydromorphone	100.00	99.66	99.63	99.74	100.37	100.55	100.21	100.74
Famotidine	100.00	99.56	99.29	99.86	99.57	99.54	99.34	100.12
Metoclopramide	100.00	99.73	99.67	99.79	100.10	100.17	99.84	100.93
Ketorolac	100.00	100.00	99.44	99.11	98.28	98.36	97.33	97.46
Mixture M4								
Hydromorphone	100.00	99.93	100.12	100.01	99.40	99.33	100.02	99.59
Famotidine	100.00	100.54	101.18	101.24	100.13	100.39	100.64	100.46
Dimenhydrinate	100.00	99.83	99.74	99.26	87.72	92.87	90.26	94.46
Haloperidol	100.00	99.89	99.99	99.88	99.04	98.93	99.60	99.40

[a]Mixture M1 was analyzed at time = 7 hours and the analysis at 4 and 8 was not done.

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Table 8. Percentages remaining of each drug in studied mixtures at 4°C.

Time (hours)	0	4	8	12	24	48	72	96
Mixture M1								
Hydromorphone	100.00	101.27[a]		100.57	100.32	102.23	102.40	100.78
Famotidine	100.00	100.94[a]		100.60	100.67	98.88	101.94	100.17
Midazolam	100.00	100.88[a]		99.93	99.29	100.92	100.51	99.88
Mixture M2								
Hydromorphone	100.00	100.63	101.14	101.27	100.58	102.03	102.84	100.74
Metoclopramide	100.00	100.91	101.49	101.77	100.69	101.19	101.83	101.19
Haloperidol	100.00	100.44	100.93	100.52	87.00	69.14	59.55	54.72
Mixture M3								
Hydromorphone	100.00	99.96	99.73	99.76	100.60	100.47	100.23	101.56
Ketorolac	100.00	99.89	99.76	99.62	99.71	99.71	99.43	100.58
Metoclopramide	100.00	100.04	99.93	99.83	100.18	100.17	100.11	101.21
Famotidine	100.00	99.93	99.65	99.92	99.90	100.05	99.73	101.48
Mixture M4								
Hydromorphone	100.00	100.43	100.40	100.53	101.28	100.59	99.79	100.44
Dimenhydrinate	100.00	99.97	100.65	100.66	91.02	82.28	81.33	87.71
Haloperidol	100.00	99.59	100.35	100.39	100.83	99.54	98.58	98.17
Famotidine	100.00	100.11	100.99	101.39	101.94	101.04	99.84	100.93

[a]Mixture M1 was analyzed at time = 7 hours and the analysis at 4 and 8 was not done.

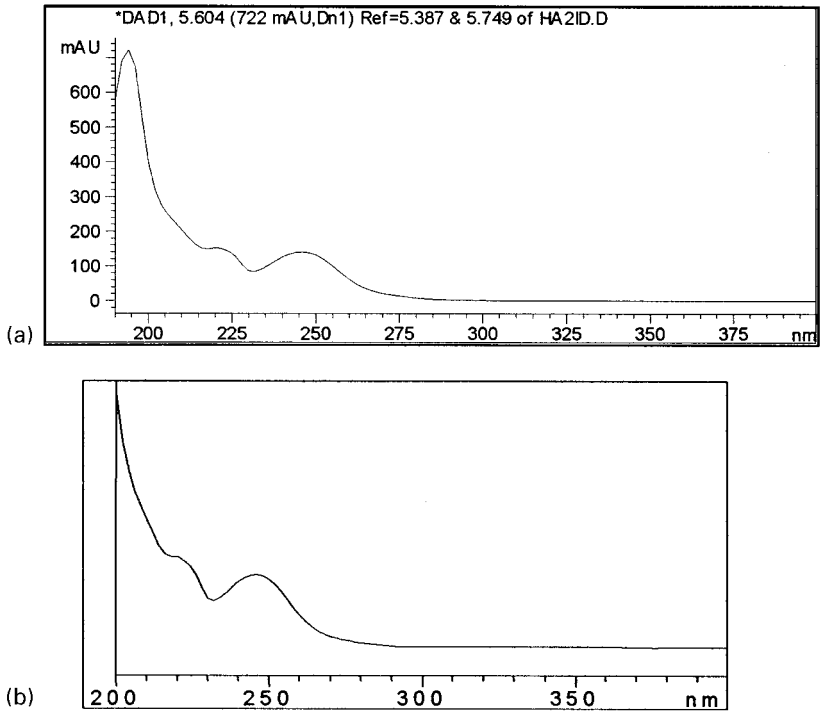

Figure 7. (a) UV spectrum of haloperidol; (b) UV spectrum of the crystal.

limit of stability after 24 hours. The precipitation of dimenhydrinate was confirmed by matching the spectra and the retention time of dimenhydrinate and the precipitate. Further studies should be performed on the physical chemistry characteristics of this mixture.

All the other mixtures were stable and compatible at 4°C and 25°C up to 96 h. Scopolamine was not analyzed. All the other mixtures were stable and compatible for 96 hours.

CONCLUSION

We succeeded in developing fast, reproducible, and robust methods to separate the active drugs and their conservatives in each mixture and to quantify those drugs. Our study is the only one that has examined the compatibility and the stability of maximal daily doses of drug mixtures for palliative care.

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Our results show that the mixtures M1 and M3 are stable and compatible for 96 hours at 4°C and 25°C. M2 is stable and compatible for 96 hours at 25°C, but it was incompatible after 12 hours when stored at 4°C. M4 was stable and compatible during 12 hours. Then, M4 was incompatible at both 4°C and 25°C.

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