Compatibility of Morphine and Midazolam or Haloperidol in Parenteral Admixtures

Michael J. LeBelle, Céline Savard and Antony Gagnon

ABSTRACT

The co-administration of parenteral medications can greatly diminish patient discomfort by eliminating the need for multiple intravenous lines. Cancer patients on long-term parenteral morphine therapy often require the additional administration of either midazolam or haloperidol.

Solutions of morphine sulfate in saline, dextrose and water were combined with commercially available midazolam or haloperidol solutions to determine the physical and chemical compatibilities of the mixtures.

A high performance liquid chromatographic method was developed for the simultaneous determination of both morphine and midazolam, and morphine and haloperidol in these solutions. Both components of mixtures of morphine and midazolam were found to be stable for up to 14 days (retention of ≥90% initial concentration) at room temperature. Mixed solutions of morphine and haloperidol, on the other hand, exhibited immediate cloudiness and eventual precipitation of a haloperidol salt which would preclude their co-administration.

Key Words: *compatibility, haloperidol, methylparaben, midazolam, morphine, propylparaben*

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RÉSUMÉ

L'administration conjointe de médicaments par voie parentérale peut réduire grandement l'inconfort des patients. On élimine ainsi le recours à des tubulures intraveineuses multiples. Les patients atteints de cancer qui reçoivent de la morphine par voie parentérale pour de longues périodes ont souvent besoin de recevoir du midazolam ou de l'halopéridol.

Du sulfate de morphine dans une solution saline, avec dextrose et eau, a été ajouté à des solutions de midazolam ou d'halopéridol disponibles sur le marché, afin de déterminer les compatibilités physiques et chimiques des mélanges ainsi produits.

On a eu recours à la chromatographie liquide à haute performance pour évaluer simultanément les mélanges morphine-midazolam, et morphine-halopéridol dans ces solutions. Les deux composantes du mélange morphine et midazolam sont restées stables pendant une période allant jusqu'à 14 jours (conservation des concentrations initiales ≥ 90 %) à la température ambiante. Les solutions de morphine et d'halopéridol sont par contre devenues immédiatement troubles et ont formé un précipité de sel d'halopéridol rendant ainsi leur administration conjointe impossible.

Mots clés : *compatibilité, halopéridol, méthylparabène, midazolam, morphine, propylparabène*

INTRODUCTION

Pain management of cancer patients often involves the administration of strong opiates, the main agent being morphine. Through direct stimulation of the chemoreceptor trigger zone for emesis, morphine may cause nausea and vomiting.[1] Hence, the addition of an antiemetic is frequently necessary. Haloperidol is one agent that has been used for this purpose. In addition to morphine, benzodiazepines are also used frequently as sedatives in cancer patients with terminal agitation. Subcutaneous or intravenous administration of all of these medications becomes necessary when the oral route of administration is no longer available or the number of venous accesses available is limited.

The stability of morphine has been confirmed both alone[2,3] and in combination with ketamine.[4] Midazolam has also been shown to be extremely stable in a number of vehicles.[5-8] The visual compatibility of midazolam and morphine as well as a number of other preoperative injectable preparations has been reported.[9] Morphine (10 mg/mL) was described as visually compatible with midazolam (5 mg/mL) for four hours at 25°C under fluorescent light based on the absence of haze, precipitate, colour change or gas production when the mixed solutions were examined with the aid of a magnifying lamp (magnification 1.77 X).

We also mixed an aqueous morphine solution (5 mg/mL) with a midazolam solution (1 mg/mL) in a 1:1 (v/v) ratio and confirmed the apparent compatibility of the mixture by visual inspection against white and black backgrounds. However, examination of this mixed solution under a microscope (400 X) using a polarized light source demonstrated the pre-

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sence of crystals. Storey et al[10] have also reported the presence of crystals in admixtures of injectable haloperidol with aqueous morphine.

We, therefore, conducted this study to determine both the chemical and physical compatibilities of morphine sulfate with the commercially available preparations of midazolam (Versed®) and haloperidol (Haldol®). Mixed solutions of morphine sulfate combined with either midazolam or haloperidol were prepared and allowed to stand at room temperature protected from light. Unfiltered and filtered solutions were analyzed periodically by high performance liquid chromatography to detect changes in concentration.

METHODS

Analytical Standards. Commercial house standards of midazolam base (Hoffmann-La Roche Ltd, Mississauga, Ont., lot 0071104) and haloperidol base (McNeil Pharmaceutical, Don Mills, Ont., expiry 08/94, no lot number) were used as received.

Stock Solutions Preparation. Six stock solutions of morphine sulfate (MacFarland Smith Ltd. lot 15270) were prepared at 10 mg/mL and 5 mg/mL in distilled water (DW), 0.9% sodium chloride (NS), and 5% dextrose in water (D5W). Versed®[a] and Haldol®[b] were used as received as the midazolam and haloperidol stock solutions.

Preparation of Solution Admixtures. An aliquot (8.0 mL) of each of the six stock solutions of morphine sulfate was combined with an equal aliquot of midazolam stock solution. An aliquot (8.0 mL) of each of the four stock solutions of morphine sulfate prepared in DW and D5W was combined with an equal volume of the haloperidol stock solution. All solution admixtures were stored in glass scintillation vials (20 mL) protected from light at room temperature (20-25°C).

Analysis of Solution Admixtures. All solutions were well mixed before sampling. From each admixture, two aliquots were taken and treated separately. One aliquot (1.0 mL) was diluted without filtration to 5.0 mL with 80:20 (v/v) acetonitrile:water. Another 1.0 mL aliquot was taken from the filtered (Millex-GS , 0.22 µm, aqueous, Millipore Products Division, Bedford, MA 01730) portion of the solution and diluted in an identical manner. Duplicate injections of each solution were made. Samples were taken as soon as possible after mixing (day 0) and on days 2 and 14.

The Analytical System. Acetonitrile (J.T. Baker, Phillipsburg, NJ, 08865) and tetrahydrofuran (Caledon Laboratories Ltd., Georgetown Ontario) were HPLC grade. Triethylamine (Aldrich Chemical Co. Inc., Milwaukee, Wi 53233) was 99+% grade. The same high performance liquid chromatographic (HPLC) system was used for the simultaneous determination of morphine and midazolam, and morphine and haloperidol. The liquid chromatograph consisted of a pump/autosampler combination (SP 8100, Spectra Physics Inc., San José, CA 95134) and a diode array detector (Hewlett Packard 1040A including a model 300 data system and 7550A graphics plotter, Hewlett-Packard Company, Mississauga, Ontario L4V 1M8). A 10-µL injection loop was installed in the autosampler. A spectrum (200 nm -400 nm) was acquired for all chromatograms. Quantification was performed using the absorbance at 254 nm. The mobile phase was pumped at 1.0 mL/min through a 4.6 mm x 25 cm reversed-phase column (Supelcosil LC-8, 5µm, Supelco Inc., Bellefonte, PA 16823-0048) at ambient temperature. The mobile phase consisted of 65% aqueous triethylamine, 1.0% v/v, pH 7.0, 25% acetonitrile and 10% tetrahydrofuran (v/v/v). The pH of the aqueous triethylamine solution was adjusted with glacial acetic acid to yield a pH of 7.0 (Digital pH Wand Model 5985-75, Cole-Palmer Instrument, Chicago, Illinois 60648); this solution was prepared daily. Other brands of tetrahydrofuran were tried and found to be unsuitable. Even using the brand specified, it must be taken from a recently opened bottle. We found that after a four liter bottle had been open for four to five months it was unsuitable. Injections using older solvent resulted in considerable baseline disruption near the solvent peak making quantification of the morphine peak difficult.

Peak Identifications. Peak identifications were performed with a gas chromatograph-mass spectrometer (Carlo Erba model 6000, Carlo Erba Strumentazione, Saddle Brook, NJ 07662 and Finnigan Model 800 Ion Trap, Finnigan Mat, San José, CA 95134-1991). The gas chromatograph was equipped with a capillary column (DB-5, 15m x 0.25 mm (0.25 µm film thickness), J&W Scientific, Folsom, CA 95630) and a split/splitless injector operated in both split mode with a split ratio of 30:1 and in splitless mode (vent closed for 30 sec). Two column conditions were used: A; the column was programmed from 100°C, after a one minute hold, to 295°C at 20°C/min; final column temperature was maintained for five minutes and B; the column was programmed from 200°C, after a one minute hold, to 300°C at 20°C/min; final column temperature was maintained for three minutes.

RESULTS

The precision of the assays for the three drug substances was less than 1% (n=5) and the coefficients of correlation of the peak areas to concentrations of all three drug

[a] Midazolam base, 5 mg/mL (Hoffmann-La Roche Ltd, Mississauga, Ontario., lots 92065 and 93062). This solution also contains[11] sodium chloride, disodium edetate, benzyl alcohol and either hydrochloric acid or sodium hydroxide.[11]

[b] Haloperidol base, 5 mg/mL (McNeil Pharmaceutical, Don Mills, Ontario., lot 62A268). This solution also contains methylparaben, propylparaben and lactic acid.[11]

substances were 0.9999 over a range that spanned 20% to 200% of the expected concentration.

Verification of Peak Integrity. The purity of the quantified drug substance peaks was verified by the use of the HPLC diode array detector and the gas chromatograph-mass spectrometer. We previously used these techniques to help confirm the purity of chromatographic peaks.[12] The UV spectra of the peaks ascribed to the three analytes were compared to spectra of the drug substances in the standard solutions. The spectra were visually coincident. The most concentrated aqueous solutions were also examined using the "peak purity" program of the diode array detector's data system. Values of 1000 indicating peak purity were obtained for all three peaks.

The GC-MS verification of peak purity involved the collection of the eluent containing each of the three drug substances at the higher morphine concentration on the last day of analysis. The solvent was completely evaporated with a stream of nitrogen. For midazolam and haloperidol, the residues were dissolved in 100 µL of methanol and injected into the chromatograph in split mode using condition A. For morphine, 100 µL of N-methyl-N-trimethylsilyl-trifluoroacetamide, MSTFA (Pierce Chemical Company, Rockford, Illinois 61105), was added, the mixture was then heated at 60°C for 15 minutes and the solution injected into the chromatograph in splitless mode using condition B. This reaction is necessary to convert morphine to a volatile derivative which may be analysed by gas chromatography.[13] The solutions of the collected midazolam and haloperidol peaks and the MSTFA reaction solution of the collected morphine peak gave only one peak each with a retention time and mass spectrum identical to that obtained using an authentic standard of the drug.

The absence of adsorption of the three drugs to the filters was confirmed by analysis of filtered and unfiltered aliquots of the morphine, midazolam and haloperidol stock solutions.

Based on the results of the peak purity determination with the diode array detector, the demonstration of single detected peaks by GC-MS of collected HPLC peaks, and the absence of absorption of the drugs on the filters used, we concluded that the method was accurate and that the method was stability indicating for all three drugs.

Morphine-Midazolam Admixtures. The solutions were clear when visually inspected against white and black backgrounds. The results of the determination of both the morphine and midazolam components in the morphine-midazolam admixtures are shown in Table I, morphine, and Table II, midazolam, respectively.

Table I. Concentrations of Morphine in Morphine Midazolam Solutions

		% Initial Morphine Concentration Remaining					
		DAY					
	Actual Initial Conc.mg/mL	0		2		14	
		F[a]	NF[b]	F[a]	NF[b]	F[a]	NF[b]
Aqueous	5.275	99.4	101.0	97.5	99.5	96.5	96.8
		99.9	101.3	97.9	98.6	96.3	96.5
	2.575	102.4	103.2	103.8	106.4	94.3	94.3
		103.5	104.0	97.8	106.8	95.3	95.5
Saline	5.060	101.3	102.2	99.0	100.2	96.0	96.6
		100.1	99.4	98.3	100.4	96.2	96.6
	2.535	105.8	105.5	97.2	99.4	92.6	93.8
		104.9	105.1	97.8	99.2	94.5	93.0
Dextrose	5.010	95.2	94.2	96.6	96.6	92.3	91.5
		93.9	94.6	96.6	97.1	92.4	92.0
	2.495	96.0	96.6	98.8	98.8	93.4	92.6
		96.0	101.8	98.8	98.8	93.6	93.2

[a] The solution was filtered before analysis
[b] The solution was not filtered before analysis

Table II. Concentrations of Midazolam in Morphine Midazolam Solutions

	% Initial Midazolam Concentration Remaining					
	DAY					
Actual Initial Conc.mg/mL	0		2		14	
	F[a]	NF[b]	F[a]	NF[b]	F[a]	NF[b]
Aqueous/Morphine (5.275 mg/mL)						
2.915	98.6	100.0	96.9	99.4	97.7	97.9
	98.2	100.5	97.4	99.4	98.1	97.9
Aqueous/Morphine (2.575 mg/mL)						
2.915	100.0	100.5	97.2	101.2	97.9	98.1
	100.1	101.0	97.2	101.3	98.1	98.1
Saline/Morphine (5.060 mg/mL)						
2.915	97.5	97.9	97.5	101.4	96.7	97.7
	98.2	97.9	97.4	101.6	97.0	98.2
Saline/Morphine (2.535 mg/mL)						
2.915	98.2	98.9	97.9	100.3	97.0	97.7
	98.2	98.9	98.1	100.3	97.0	97.5
Dextrose/Morphine (5.010 mg/mL)						
2.380	98.8	100.2	98.7	98.7	96.8	98.8
	99.1	100.0	98.5	99.2	96.6	96.4
Dextrose/Morphine (2.495 mg/mL)						
2.380	100.4	101.5	98.5	97.9	92.6	95.6
	100.2	101.3	98.7	97.9	92.4	95.6

[a] The solution was filtered before analysis
[b] The solution was not filtered before analysis

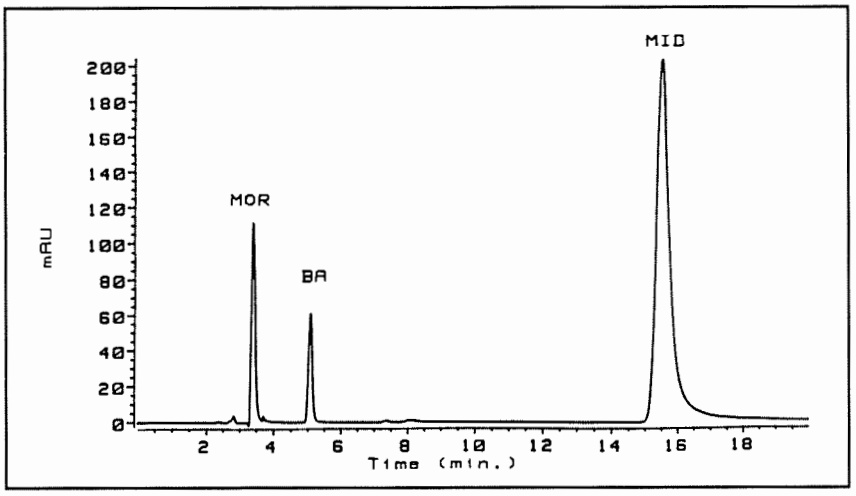

Figure 1: HPLC chromatogram of a 14 days-old morphine-midazolam combination solution. Peak identification: MOR, morphine; BA, benzyl alcohol; MID, midazolam.

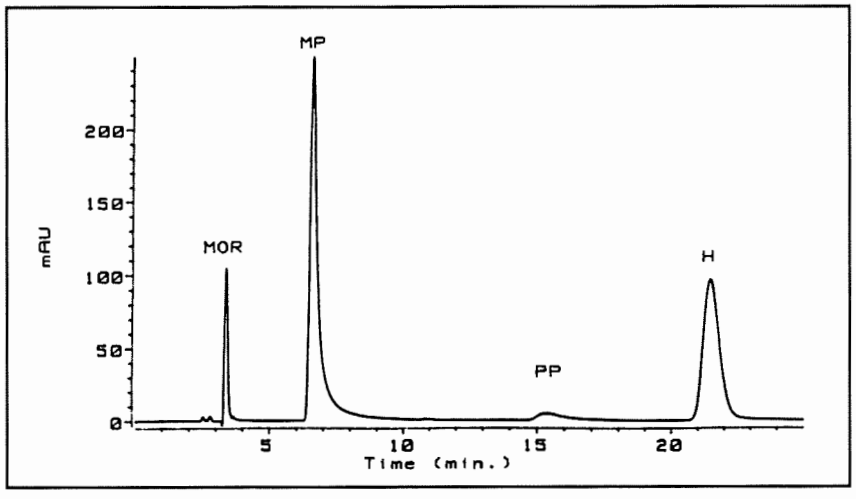

Figure 2: HPLC chromatogram of a 1 day-old morphine-haloperidol combination solution. Peak identification: MOR, morphine; MP, methylparaben; PP, propylparaben; H, haloperidol.

Figure 1 shows the chromatogram of the 14 days-old morphine-midazolam combination solution. Morphine (MOR) and midazolam (MID) eluted at 3.4 and 15.5 min respectively. The peak at 5.1 min is benzyl alcohol (BA), a preservative in Versed®. This was confirmed by injection of an authentic standard (Aldrich Chemical Co. Inc., Milwaukee, Wi 53233).

Morphine-Haloperidol Admixtures. Cloudiness developed immediately when the haloperidol solution was added to the morphine sulfate solution. Crystal formation was visually detectable after 24 hours and increased on subsequent days. The results of the determination of the residual concentrations of the morphine and haloperidol in these solutions are shown in Table III, morphine, and Table IV, haloperidol, respectively.

Figure 2 shows the chromatogram of a morphine-haloperidol combination solution. The haloperidol (H) eluted at 21.5 min. The two additional peaks in the chromatogram are methylparaben (MP, 6.6 min.) and propylparaben (PP, 15.4 min.), preservatives in the commercial Haldol® solution These retention times were confirmed by injection of authentic standards (Aldrich Chemical Co. Inc., Milwaukee, Wi 53233).

The pH of all of the mixed solutions was monitored over the study and no changes were detected. This indicates that the precipitation that occurred in the morphine-haloperidol mixed solutions was not due to perturbation of the pH of the Haldol® solution. The commercial solution had an initial pH of 3.22 and the mixed solutions had pHs only slightly above, 3.3, which is within the manufacturer's specifications[11] (3.2 to 3.8).

The precipitate formed in the morphine-haloperidol solutions was identified by the combination of HPLC and gas chromatography-mass spectrometry. The precipitate that had formed in the most concentrated aqueous morphine-haloperidol combination solution was isolated by filtration under vacuum. It was washed with cold water and then dried under vacuum (0.1 mm Hg) overnight. The melting point of the friable white solid was 136-170°C. It was not readily soluble in chloroform but dissolved in methanol and acetonitrile. A small portion of the solid was dissolved in the mobile phase used for HPLC and injected into the instrument. Three peaks were detected; they had the same retention times as methylparaben, propylparaben and haloperidol. No morphine was detected which agreed with the results from the determination of the drug concentrations in the combination solutions which indicated that the morphine had remained in solution.

A small amount of the precipitate was also dissolved in ethyl acetate and injected into the GC-MS. Figure 3 shows the resulting reconstructed ion chromatogram (RIC). Peaks 1 and 2 are methyl- and propylparaben, respectively. Peak 3 is haloperidol. Mass spectra and retention times of these peaks were confirmed by the injection of authentic standards. We conclude, therefore, that the precipitate resulting from admixture of the morphine and haloperidol solutions was a combined methyl- and propylparaben salt of haloperidol.

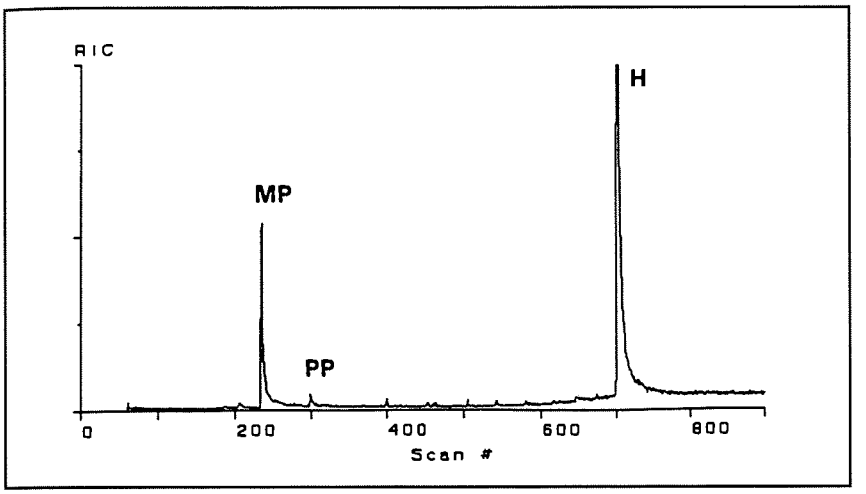

Figure 3: Reconstructed ion chromatogram (RIC) of the precipitate formed on admixture of morphine and haloperidol. Peak identification: MP, methylparaben; PP, propylparaben; H, haloperidol.

Table III: Concentrations of Morphine in Morphine Haloperidol Solutions

		% Initial Morphine Concentration Remaining			
		DAY			
	Actual Initial Conc.mg/mL	0		3	
		F[a]	NF[b]	F[a]	NF[b]
Aqueous	5.535	101.2	100.9	106.0	ND[c]
		101.3	102.2	105.0	–
	2.550	96.4	93.1	96.2	–
		95.2	96.4	94.1	–
Dextrose	5.365	95.4	98.3	95.5	–
		96.3	98.6	97.2	–
	2.585	97.6	97.4	95.9	–
		97.2	99.0	95.3	–

[a] The solution was filtered before analysis
[b] The solution was not filtered before analysis
[c] Not determined, see text.

DISCUSSION

High performance liquid chromatography was chosen for the analysis of the solutions as it was considered the only analytical method to permit the simultaneous quantification of all three drugs substances without derivatization.[2] This system was adapted from one routinely used in our laboratory for the quantification of some alkaloids. In order to determine possible physical interactive phenomena such as agglutination or salt formation with subsequent crystallization the solutions were filtered through 0.22 μm filters. This filter size was chosen to represent particle size pass criteria which would have little physiological impact. At the same time it would remove from the solutions, before quantification, visually undetected particulate matter.

Admixture solutions were prepared using morphine in DW to determine if the interaction between the morphine and midazolam that was observed using microscopy and polarized light and that between morphine and haloperidol were due to the sodium chloride or dextrose in the other vehicles studied.

Morphine-Midazolam Admixtures. The morphine-midazolam solutions showed good stability (≥90% of initial). Small differences were detected in the residual concentrations between the filtered and unfiltered aqueous and NS solutions of both the morphine and midazolam on day 2. For example, the morphine concentration, Table I, of the unfiltered aqueous solution prepared at 5.275 mg/mL (99.1±0.45) was greater than that found for the filtered solution (97.7±0.20). Similar differences can be seen in the other corresponding filtered and unfiltered solutions prepared in these two vehicles on this day. The midazolam concentrations for these solutions, Table II, also reveal differences between the filtered and unfiltered solutions. However, the results obtained on day 1 and day 14 in Tables I and II show no differences between the filtered and unfiltered solutions. Although these differences cannot be confirmed as statistically significant they are consistent with our observation, using microscopy and polarized light, of fine crystals in morphine-midazolam combination solutions. This may be an indication that a small amount of precipitation occurred which was followed by re-solubilization of the precipitate. The amount of morphine and midazolam lost due to this unconfirmed phenomenon is not clinically significant.

Morphine-Haloperidol Admixtures. Cloudiness was immediately evident when the morphine and haloperidol solutions were mixed. This observation of an almost immediate precipitation in these solutions is reflected in the assay results. On day 0, little difference was detected in the concentrations of the morphine in the filtered and unfiltered solutions, Table III. However, the haloperidol results were considerably different. For example, the assay results for haloperidol in the filtered aqueous solutions were about 2% lower than those for the unfiltered solutions Table IV. The difference between the filtered and unfiltered solutions was even more evident in the case of the combination solutions prepared in D5W. The two filtered

aliquots gave results that were about 4% lower than those of the two unfiltered aliquots. The crystalline precipitate was allowed to continue to form and the solutions were re-analyzed on day 3. Only filtered solutions were analyzed because taking a sample from a solution containing such a significant amount of large particles would only lead to spurious results. The analysis of the filtered solutions was intended to aid in identifying the nature of the precipitate. In fact, it can be seen from the results in Table III that the concentrations of the morphine on this day did not differ significantly, in either the DW or the D5W solutions, from the concentrations that had been detected on day 0. The concentration of the haloperidol in both solutions, on the other hand, had decreased by approximately 50%, Table IV. These results alone, therefore, implied that the precipitate was composed of only the haloperidol component of the morphine-haloperidol combination solution. This was confirmed by both the HPLC and GC-MS results which indicated that the precipitate was composed of only haloperidol and the methyl- and propylparaben. These conclusions differ from those previously reported.[10] The same commercially available injectable haloperidol diluted with aqueous morphine or hydromorphone solutions yielded a precipitate composed only of haloperidol base.

In conclusion, morphine at concentrations of 2.5 and 5 mg/mL is compatible with midazolam at a concentration of 2.5 mg/mL when mixed in NS or D5W. These solutions are stable for a period of 14 days at room temperature protected from light with more than 90% of each drug remaining in solution. However, filtration of the mixed solutions immediately before administration is recommended because of the observation, using microscopy, of the presence of crystals in these mixed solutions.

The administration of undiluted combined morphine and Haldol solutions over the concentration ranges studied is not possible. Precipitation of a significant fraction of the haloperidol precludes co-administration.

Our observations also demonstrate that only low-magnification examination[9] of drug solution admixtures is not sufficient to demonstrate drug compatibilities. Although the particle size of the observed crystals in the morphine-midazolam solutions was not determined, the small differences observed between the filtered and unfiltered admixtures of these drug substances imply that at least some of the particles were larger than 0.22 μm.

Table IV: Concentrations of Haloperidol in Morphine Haloperidol Solutions

Actual Initial Conc.mg/mL	% Initial Haloperidol Concentration Remaining DAY 0 F[a]	0 NF[b]	3 F[a]	3 NF[b]
Aqueous/Morphine (5.535 mg/mL)				
2.580	95.9	97.6	45.8	ND[c]
	95.3	97.6	45.6	–
Aqueous/Morphine (2.550 mg/mL)				
2.580	96.7	98.2	56.1	–
	96.8	98.8	55.9	–
Dextrose/Morphine (5.365 mg/mL)				
2.580	90.6	94.9	43.3	–
	90.8	94.9	43.3	–
Dextrose/Morphine (2.585mg/mL)				
2.580	96.7	101.7	57.0	–
	97.0	100.9	57.0	–

[a] The solution was filtered before analysis
[b] The solution was not filtered before analysis
[c] Not determined, see text.

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