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Chemical stability of morphine and methadone, and of methadone in combination with acepromazine, medetomidine or xylazine, during prolonged storage in syringes

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Objective To assess the chemical and physical stability of morphine and methadone stored in syringes for 12 months and of methadone when mixed with acepromazine, medetomidine or xylazine.

Methods A high-performance liquid chromatography (HPLC) technique was developed and validated for the analysis of morphine and methadone. Morphine and methadone were dispensed into syringes and stored at 25°C/60% relative humidity (RH) and 40°C/75% RH. Solutions containing mixtures of methadone combined with acepromazine, medetomidine or xylazine were stored in syringes at 25°C/60%RH. At initiation, after 1 week and then 1, 3, 6, 9 and 12 months, samples were analysed by HPLC for the quantification of the morphine or methadone. Measured concentrations were assessed as a function of storage time and temperature using linear regression statistics to calculate stability.

Results When stored at 40°C/75%RH as pre-dispensed syringes, severe physical and chemical changes were observed after the third month for both morphine and methadone. In contrast, at 25°C/60%RH both drugs remained chemically stable for 12 months, with concentration variations not exceeding a 5% change from initiation as stipulated in VICH stability guidelines. When in combination with acepromazine or xylazine, methadone also remained chemically stable, but the combination with medetomidine failed stability criteria prior to 6 months. Precipitation compromised the physical stability of methadone in all unsealed syringes prior to 9 months' storage.

Conclusion Pre-dispensing morphine or methadone into unsealed syringes compromises the drugs' physical stability. Mixing of methadone with other drugs can degrade its chemical stability.

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Keywords acepromazine; drug storage; methadone; morphine; medetomidine; stability; xylazine

Abbreviations RH, relative humidity; UV, ultraviolet; Vis, visible

Morphine and methadone are μ -opioid agonists used in veterinary practice to provide analgesia. Opioids and sedatives are often combined within a syringe and then administered as premedication to animals prior to anaesthesia and surgical procedures. Many different premedication combinations are recommended in small animal medicine and one of the more popular combinations is acepromazine and an opioid.¹ Acepromazine is a phenothiazine derivative used to provide mild to moderate sedation in patients and has synergistic effects when combined with opioids. Other commonly used premedications include $\pm_2$ -adrenergic agonists such as medetomidine and xylazine, which can be combined with opioids to provide sedation and analgesia.²

Morphine and methadone are both classified as Schedule 8 poisons ‘drugs of addiction’, according to the Australian *Poisons Standard* and have specific requirements related to their handling and storage; that is, storage in a locked cabinet and strict records of any drug dispensed or destroyed by authorised persons.

Prior to registration, pharmaceuticals must undergo rigorous stability testing to determine the shelf life when stored in their original packaging.³ However, there have been limited studies looking into the stability of these products when stored in non-original packaging. In addition, some practitioners may pre-dispense and combine pharmaceuticals into mixtures and store them in non-original packaging to allow for quick administration of medication mixtures. To the authors’ knowledge, the stability of frequently-used mixtures of morphine or methadone has not been evaluated.

Pharmaceutical stability testing evaluates three distinctly separate product characteristics: physical stability, chemical stability and sterility. For the physical characteristics, a drug product is observed for noticeable changes such as colour, turbidity or viscosity. The chemical stability of a drug product is assessed over time for changes in the molecular structure of the parent active compound, and sterility testing assesses the ability of contaminating microorganisms to survive and replicate in the formulation.³

This study was divided into two parts. The first aimed to evaluate the chemical and physical stability of morphine and methadone once dispensed and stored in syringes. The second aim of this study was to investigate the chemical and physical stability of methadone when dispensed into syringes in mixed combinations with acepromazine, medetomidine or xylazine. The objective of this project was to emulate clinical practice, thus providing guidance to clinicians on whether pre-dispensing morphine or methadone affects their physical or chemical stability.

We hypothesised that following 12 months of storage after being dispensed from their original packaging, the concentrations of morphine and methadone alone or in combination would not differ from their concentrations at initiation.

Materials and methods

Chemicals and reagents included methadone hydrochloride (Physeptone® 10 mg/mL, GlaxoSmithKline Australia Pty Ltd; Methodyne® 10 mg/mL, Jurox Pty Ltd); morphine sulfate (DBL® 10 mg/mL, Hospira Pty Ltd); acepromazine (Acepril® 10 mg/mL, Troy Laboratories Pty Ltd); medetomidine (Dormitor® 1 mg/mL, Orion Pharma); xylazine (Xylazil® 20 mg/mL, Troy Laboratories Pty Ltd); acetonitrile and sodium acetate (Merck); glacial acetic acid and sodium dodecyl sulfate (Sigma-Aldrich); and sodium hydroxide (Asia Pacific Speciality Chemicals Ltd). All reagents were of analytical grade except acetonitrile, which was HPLC grade. Water for injection (type II) was used throughout and prepared using reverse osmosis and double distillation.

Study 1: pre-dispensed morphine and methadone

Morphine and methadone (Physeptone®) were prepared using the same method. A 1-mL volume was withdrawn from the original packaging into a 1-mL tuberculin syringe (BD Australia) using 1-inch hypodermic 21G needles (Nipro Australia Pty Ltd). The syringes were labelled and the needle was re-capped. Syringes were stored on their side in a metal box in stability cabinets set and maintained at 25°C (n = 14) and 40°C (n = 10) with a relative humidity (RH) of 60% or 75%, respectively.

Two syringes of each drug were analysed at each time point (Table 3) and two analytical samples were prepared for HPLC from each syringe. Control samples for morphine and methadone were dispensed directly from the manufacturers' packaging at each time point. Both the control and samples for both morphine and methadone were volumetrically prepared at each time point by dilution to 0.2 mg/mL in water and directly assayed by HPLC. Stability was evaluated by comparing the sample concentration to the control and the relative concentrations calculated in comparison with D0.

Study 2: pre-dispensed methadone in combinations

To ensure a uniform concentration across all samples, methadone (Methodyne®), acepromazine, medetomidine and xylazine were dispensed into sterilised glass beakers under a laminar flow hood from their original packaging to create stock solutions. From the stock solutions methadone and acepromazine, medetomidine or xylazine were transferred and combined in separate sterilised glass beakers to produce the solution mixtures (Table 1). The 14 10-mL volumes were each drawn into a 10-mL syringe (BD Australia) using 1-inch hypodermic 21G needles. The needles were re-capped and the syringes were labelled and stored on their side in a metal box in a stability cabinet set and maintained at 25°C with 60% RH.

The combination samples were prepared for analysis at each time point by selecting one 10-mL syringe and then transferring two aliquots from the syringe and diluting with water using a 10-mL volumetric flask to achieve a nominal final methadone concentration of 1.0 mg/mL. At each time point the freshly dispensed control samples for methadone were also diluted with water to achieve a 1.0 mg/mL concentration using a 10-mL volumetric flask. Stability was evaluated by comparing the sample concentration to the control and the relative concentrations calculated in comparison with D0.

Schedule of analytical determinations

The duration was chosen because regulatory guidelines for chemical stability usually work in 6 months (temporary) then 12 months or longer periods for shelf life determinations. The assays were performed according to the VICH stability testing guidelines using the minimum required time periods to satisfy the requirements for long-term (12 months) and accelerated (6 months) studies.³

For the long-term studies the time points of analysis were day 0 (D0), week 1 (W1) and months 1, 3, 6, 9 and 12. For the accelerated studies the time points of analysis were planned at D0, W1, 1, 3 and 6 months. At each time point the samples were analysed for chemical stability by HPLC and for physical stability, observable changes, including colour and loss of contents, were noted.

HPLC assay procedure

Two HPLC systems were used during this study: a Waters Alliance 2695 separation module with a 2996 PDA or 2487 dual wavelength (») absorbance detector and a Shimadzu Nexera LC-30AD solvent deliver module with SPD-m20A PDA or SPD-20 A UV-Vis detector. The detectors were set at a wavelength of 254 nm for the methadone samples and 285 nm for the morphine samples. Separation of methadone from formulation matrices was achieved using a reverse-phase XTerra phenyl 3.5 μm (150 $\times$ 4.60 mm ID) column, while separation of morphine from its matrix used a reverse-phase Luna C18 5.0 μm (250 $\times$ 4.60 mm ID) column. The mobile phases were prepared as outlined in Table 2. The HPLC flow rate was 1.0 mL/min. The column temperature was maintained at 30°C for methadone samples and 25°C for morphine samples. The assays were both validated for linearity, accuracy, repeatability and lower limit of quantification. The lower limit of quantification for the assays for methadone on the Waters Alliance and Shimadzu Nexera systems were 3.8 and 1.1 mg/mL, respectively.

For the combination study (Study 2), although the analytical method for methadone, which used a mobile phase of acetonitrile and 0.2 mol/L KH_2PO_4 buffer at pH 5.5 (50 : 50, v/v), provided sufficient separation of methadone from medetomidine and xylazine, an alternative validated method for the separation of methadone from acepromazine was required, which used acetonitrile and 0.2 mol/L KH_2PO_4 buffer at pH 7.5 (40 : 60, v/v), to facilitate quantification.

Statistical analysis

Stability was calculated using linear regression analysis of the analyte concentration as a function of time. The 90% prediction interval for the regression line was the predetermined boundary for declaration of chemical stability.

Results

Physical stability

In Study 1, noticeable physical changes were observed at each time point. At month 9 the methadone syringes stored at 25°C/60%RH had low quantities of white precipitate present at the needle hub and bevel. No observable changes occurred with the morphine samples at 25°C/60%RH. For morphine and methadone stored at 40°C/75%RH, at 3 months there was

an observable white crystalline precipitate at the needle hub and bevel, as well as yellow discolouration of the contents.

Chemical stability

Results of the chemical stability evaluation are shown in Table 3. The 90% prediction interval for stability of the analytes in studies 1 and 2 are illustrated in Figures 1 and 2, respectively. Morphine concentration remained within the acceptable criteria range over the 12 months when stored at 25°C/60%RH. Methadone concentration also remained within the acceptable criteria range, but steadily increased over the 12 months when stored at 25°C/60%RH.

When stored in mixture with xylazine, methadone remained chemically stable for 12 months. However, methadone in combination with acepromazine or medetomidine was chemically stable for only 9 and 3 months, respectively.

The accelerated chemical stability studies for morphine and methadone, which were conducted at 40°C/75%RH, resulted in marked increases in drug concentrations that exceeded the acceptable range within 3 months. Because of the severity of both the chemical and physical changes at month 3 the accelerated studies were discontinued.

In Study 2, at the 9-month time point there was evidence of low quantities of precipitate at the needle bevel for all methadone-combination sample syringes.

Discussion

We hypothesised that morphine and methadone concentrations would remain stable over a 12-month period when stored in syringes alone or, for methadone, when in combination with other sedatives. For the combinations of methadone with acepromazine, medetomidine or xylazine the dose rates used for the preparation of the pharmaceutical mixtures were based on recommended dose rates.⁴ Combinations at other concentration ratios may have different stability characteristics.

Other have also demonstrated the formation of precipitate in pre-dispensed syringes of morphine when stored at 40°C for 3 months.⁸ Therefore, storage of these drugs at temperatures approaching 40°C/75%RH compromises their physical and chemical stability. In the studies conducted at 25°C/60%RH the chemical stability remained acceptable over the full 12-month duration. However, the drugs' concentrations over this time period slightly increased and marked changes were observed in the physical stability of the methadone formulations, with crystallisation at the solvent surface at 9 months likely caused by evaporation of the formulations' solvent. To emulate clinical practice, air tight seals were not used in our study design, permitting evaporation of the syringes' contents. These results demonstrated that the clinical practice of pre-dispensing morphine or methadone into unsealed syringes cannot be condoned.

To the authors' knowledge there have been no studies published that describe the stability of methadone during prolonged storage in syringes. One study found that morphine was stable for a period of 3 months when stored in PVC containers at 22°C⁸ and another concluded that diluted morphine was stable for 2 years when stored within polypropylene syringes.⁵ Those studies determined that when stored under appropriate conditions morphine remains physically and chemically stable. Our results confirm the previous studies and provide further evidence for the chemical stability of morphine during storage in syringes. Unfortunately,

when stored in syringes lacking airtight seals, or when stored at temperatures above 25°C, the changes in drug concentration or physical characteristics are sufficient to preclude use.

In the studies performed with methadone in combination with acepromazine, medetomidine and xylazine, only the chemical stability of methadone was analysed. The chemical stability of the sedatives was not evaluated; new chromatographic methods would need to be developed and validated to evaluate this.

Although the results for methadone in combination with acepromazine indicated that the methadone was chemically and physically stable for at least 6 months, in combination with medetomidine it did not remain chemically stable. The lower confidence interval of the prediction line for methadone concentration dropped below the acceptable 5% change prior to 6 months. Therefore, we concluded that this combination is not chemically stable. The reasons for this were beyond the scope of our investigation, but our data suggested that this combination should not be stored for more than 3 months because chemical instability is likely.

When mixed in combination with xylazine we found that the recorded concentration of the methadone at D0 was 95.5% of the nominal expected concentration. When compared with W1 time point, the results recorded remained relatively constant, with a maximum variation of 2.6% from the control. We concluded that it was likely there was an analytical error at the initiation time point. This apparent error may have been associated with inaccurate sample preparation or other laboratory error prior to HPLC analysis. Irrespective of this first time point, the methadone concentration in this combination rose slightly with time, possibly because of solvent evaporation, and the methadone was demonstrated to remain chemically stable until 12 months.

Study limitations

A weakness of this study was that the chemical stability of acepromazine, medetomidine and xylazine when each was combined with methadone was not examined, so recommendations on the storage of these combinations cannot be made without further research. Additionally, the potential for breakdown of compounds that might result from storage outside of the manufacturers' recommendations was not investigated. Finally, this study did not examine the sterility of formulations or the mixtures used, so the microbiological burden of the formulations and mixtures during dispensing and at subsequent time points is unknown. Although the data supported the conclusion that morphine can be stored in syringes without significant changes in chemical stability for up to 12 months, the physical stability of methadone when similarly stored alone or in combination with other drugs was less than 9 months.

Conclusion

Our study demonstrated that methadone formulations stored in syringes at 25°C/60%RH, may be usable at a later date, up to 6 months. To reduce the effects of evaporation and crystallisation, and to prevent microbial contamination, it is recommended to seal the syringes. Nevertheless, the prudent recommendation remains unchanged; drugs should be dispensed only when required, paying specific attention to the regulatory requirements for storage and handling of these Schedule 8 drugs of addiction.

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References

1. Nicholson A, Watson A. Survey on small animal anaesthesia. *Aust Vet J* 2001;79:613–619.
2. Hall LW, Clarke KW, Trim CM. *Veterinary anaesthesia*. 10th edn. WB Saunders, London, 2001.
3. VICH. *Stability testing of new veterinary drug substances and medicinal products (Revision)*. VICH GL3(R). Brussels, 2007.
4. Tranquilli WJ, Thurmon JC, Grimm KA. *Lumb and Jones' veterinary anesthesia and analgesia*. 4th edn. Blackwell Publishing, Ames, 2007.
5. d'Hayer B, Vieillard V, Astier A et al. Stability-indicating HPLC assay and stability study over two years of morphine hydrochloride diluted solutions in polypropylene syringes. *Pharm Anal Acta* 2013;4:205.
6. Nguyen-Xuan T, Griffiths W, Kern C et al. Stability of morphine sulfate in polypropylene infusion bags for use in patient-controlled analgesia pumps for postoperative pain management. *Int J Pharm Compd* 2006;10:69–73.
7. Hung CT, Young M, Gupta PK. Stability of morphine solutions in plastic syringes determined by reversed-phase ion-pair liquid chromatography. *J Pharm Sci* 1988;77:719–723.
8. Vermeire A, Remon JP. The solubility of morphine and the stability of concentrated morphine solutions in glass, polypropylene syringes and PVC containers. *Int J Pharm* 1997;146:213–223.

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Figure 1. Mean relative concentration (percent of the nominal concentration, n = 2 per time point) for morphine (A) and methadone (B) stored in syringes at 25°C and relative humidity of 60% over 12 months. The solid line shows the linear regression and the dashed lines are the 90% confidence interval. The dotted lines at 95% and 105% represent the specification acceptance interval.

Figure 2. Mean relative concentration (expressed as a percent of the nominal concentration, n = 2 per time point) for methadone when stored in combination with acepromazine (A), medetomidine (B) and xylazine (C) at 25°C and relative humidity of 60% over 12 months. The solid line shows the linear regression and the dashed lines are the 90% confidence interval. The dotted lines at 95% and 105% represent the specification acceptance interval.

Table 1. Preparation^a of mixture samples containing methadone and sedatives (acepromazine, medetomidine and xylazine)

Concentration in mixture (mg/mL)				Volume used in stock solutions methadone : sedative (mL)
Methadone	Acepromazin e	Medetomidin e	Xylazi ne	
8.33	1.69			133 : 27
7.14		0.28		114 : 46
6.66			6.63	107 : 53

^aVolume rounded to the nearest whole number to assist with sample uniformity.

Table 2. High-performance liquid chromatography mobile phase composition for the analytical samples

Analytical sample	Mobile phase composition	pH ^a
Mobile phases	A: Acetonitrile B: 0.5 mol/L acetate buffer made by dissolving 1.457 g of sodium dodecyl sulfate in 625 mL of water with 5.683 g of ammonium acetate and 13.7 mL of acetic acid added in accordance to previously published method ⁵ C: 0.02 mol/L mono-potassium phosphate made by dissolving 2.72 g KH ₂ PO ₄ in 1 L of water	
Morphine	A/B 37.5%/62.5% (v/v)	4.2
Methadone	A/C 50%/50% (v/v)	7.5
Methadone when mixed with		
Acepromazine	A/C 40%/60% (v/v)	5.5
Medetomidine or Xylazine	A/C 50%/50% (v/v)	7.5

^apH adjusted using 1.0 mol/L NaOH and all mobile phases were filtered through 0.2-μm nylon filters.

Table 3. Relative concentrations of morphine and methadone in comparison with control, when stored in syringes on their side in a metal box in stability cabinets set and maintained at 25°C and 40°C (accelerated), with a relative humidity of 60% or 75%, respectively

Analytical sample	Concentration of analytes compared with standard (%)						
	T0	Week 1	Month				
			1	3	6	9	12
Morphine	100.3	102.5	102.0	103.1	100.3	103.9	101.73
Morphine (accelerated)	100.3	99.9	108.2	123.8	*	*	*
Methadone	97.5	95.8	96.9	99.4	96.5	102.44	97.29
Methadone (accelerated)	97.5	98.8	101.9	101.1	*	*	*
Methadone with acepromazine	97.3	99.2	99.8	98.5	99.6	97.31	94.82
Methadone with medetomidine	99.3	100.1	98.0	99.7	95.3	92.52	90.93
Methadone with xylazine	95.5	99.3	101.3	102.3	100.6	97.97	100.77

*Concentration results from the accelerated studies, conducted at 40°C with a relative humidity 75% were discontinued after 3 months.

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Title:

Chemical stability of morphine and methadone, and of methadone in combination with acepromazine, medetomidine or xylazine, during prolonged storage in syringes

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