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Stability of oxycodone solutions containing *S*-ketamine or dexmedetomidine

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ABSTRACT

Objectives To determine whether adding *S*-ketamine or dexmedetomidine to oxycodone affects the microbiological, physical or chemical stability of patient-controlled analgesia (PCA) solutions prepared in a hospital pharmacy.

Methods Oxycodone solution (1 mg/mL) and three oxycodone–*S*-ketamine mixtures (0.25, 0.50, 0.75 mg/mL) and three oxycodone–dexmedetomidine mixtures (2.5, 5.0, 10 µg/mL) were compounded under validated European Union Good Manufacturing Practice (GMP) Class A/B aseptic conditions and filled into PCA reservoirs. Reservoirs (n=42 for physicochemical studies, n=21 for sterility, n=4 for antimicrobial activity testing) were stored at 2–8°C for 28 days, then at 20–25°C for 2 days. Sterility was assessed by membrane filtration according to European Pharmacopoeia Section 2.6.1 (Ph. Eur. 2.6.1). Physical stability was evaluated by visual inspection, pH, weight and osmolality. Chemical stability was assessed using a validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method developed in accordance with US Food and Drug Administration (FDA) and International Conferenece on Harmonisation (ICH) Q2(R1) guidelines.

Results All antimicrobial activity tests showed growth of the six reference strains, indicating no inhibition by the drug mixtures. All 21 sterility-test reservoirs remained free of turbidity throughout 30 days. No visual changes, precipitation or discolouration were observed. Weight loss was ≤0.3%, pH changes were within the required range of 4.5–7 and osmolality increased by <1.4% during the study. Measured oxycodone, *S*-ketamine and dexmedetomidine concentrations remained within ±5% of initial values, and no degradation products were detected.

Conclusions Oxycodone PCA solutions containing *S*-ketamine or dexmedetomidine remained sterile, physically stable and chemically stable for 28 days at 2–8°C followed by 2 days at room temperature at 20–25°C. These findings support the potential for extended shelf life and centralised batch preparation of opioid–adjuvant PCA reservoirs in hospital pharmacy practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Opioid–adjuvant combinations such as oxycodone with *S*-ketamine or dexmedetomidine are increasingly used in patient-controlled analgesia (PCA), but no commercial multi-agent formulations exist. Hospital pharmacies therefore prepare these mixtures as compounded sterile preparations, despite limited data on their chemical and microbiological stability.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that oxycodone PCA solutions containing *S*-ketamine or dexmedetomidine remain chemically stable and microbiologically sterile for 28 days at 2–8°C plus 2 days at 20–25°C, when prepared under validated aseptic conditions. Concentrations of all analytes remained within ±5% of initial values, and no degradation products were detected using a validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These stability data support the assignment of extended beyond-use dates and enable centralised batch compounding of PCA reservoirs in hospital pharmacies. The findings have the potential to reduce aseptic workload, improve production efficiency and decrease medication waste, while ensuring product quality.

INTRODUCTION

Opioids have long been the cornerstone of postoperative pain management but concerns over adverse effects and opioid-related harms have driven increasing interest in multimodal analgesia strategies.[1–3] Patient-controlled analgesia (PCA) enhances pain management by allowing patients to self-administer medication on demand, which often improves patient satisfaction and analgesic control.[4 5] In clinical practice, adjuvant agents such as *S*-ketamine and dexmedetomidine are increasingly combined with opioids in PCA to improve analgesia and reduce opioid requirements.[6–10]

However, opioid formulations containing adjuvant drugs are not commercially available. Hospital pharmacies therefore must prepare these mixtures as compounded sterile preparations (CSPs), a process that is technically demanding and subject to strict quality standards.[11 12] For such preparations, reliable data on chemical stability, chemical integrity and microbiological sterility are essential to assign appropriate shelf lives, ensure patient safety and support efficient production workflows.

Despite the growing clinical use of opioid–adjuvant PCA mixtures, systematic stability data for combinations of oxycodone with *S*-ketamine or with dexmedetomidine remain limited. For hospital pharmacies, this lack of evidence restricts the ability

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Table 1 Patient-controlled analgesia reservoirs containing mixtures of oxycodone, dexmedetomidine and *S*-ketamine

Mixture	Oxycodone 10 mg/mL (mL)	Dexmedetomidine 100 µg/mL (mL)	S-Ketamine 25 mg/mL (mL)	Sodium chloride solution 9 mg/mL (0.9%) (mL)
Oxycodone 1 mg/mL+dexmedetomidine 2.5 µg/mL	10	2.5	–	87.5
Oxycodone 1 mg/mL+dexmedetomidine 5.0 µg/mL	10	5.0	–	85
Oxycodone 1 mg/mL+dexmedetomidine 10.0 µg/mL	10	10.0	–	80
Oxycodone 1 mg/mL+*S*-ketamine 0.25 mg/mL	10	–	1	89
Oxycodone 1 mg/mL+*S*-ketamine 0.5 mg/mL	10	–	2	88
Oxycodone 1 mg/mL+*S*-ketamine 0.75 mg/mL	10	–	3	87

to conduct batch preparation, optimise aseptic workflow and minimise medication waste. Stability and sterility studies specific to these clinically relevant combinations are therefore needed to guide safe compounding practices and storage conditions.

The aim of the present study was to evaluate the chemical, physical and microbiological stability of oxycodone PCA solutions combined with *S*-ketamine or dexmedetomidine when prepared under validated aseptic conditions and stored in PCA reservoirs under clinically relevant conditions. For this purpose, we first developed and validated a method for determination of concentrations of oxycodone together with *S*-ketamine or dexmedetomidine. Subsequently, we performed a shelf-life study with different combinations of these three drugs used in pain treatment.

MATERIALS AND METHODS

Sample preparation

Description of the drugs, reference solutions and other materials are given in the online supplemental Text. Oxycodone solution (1 mg/mL as oxycodone hydrochloride trihydrate) was prepared by diluting 10 mL of the pharmaceutical product (Oxanest 10 mg/mL) into a syringe containing 90 mL of 9 mg/mL (0.9%) sodium chloride solution. Three different mixtures of oxycodone and *S*-ketamine were prepared by mixing known amounts of the pharmaceutical products (Oxanest 10 mg/mL and Ketanest-S 25 mg/mL) in syringes containing 9 mg/mL (0.9%) sodium chloride solution (table 1). Similarly, three different mixtures of oxycodone and dexmedetomidine were prepared by mixing known amounts of the pharmaceutical products (Oxanest 10 mg/mL and Dexdor 100 µg/mL) in syringes containing 9 mg/mL (0.9%) sodium chloride solution (table 1).

Sample storage

PCA reservoirs were stored for up to 28 days at 2–8°C in a refrigerator approved for hospital use. Thereafter, they were transferred to room temperature (20–25°C) for 2 days. The refrigerator was equipped with an automated temperature monitoring system. The PCA reservoirs were protected from light.

The stability of the drug solutions was investigated by analysing samples taken after different periods of storage, on seven different days (days 0, 3, 7, 14, 21, 28 and 30 of the stability test). The study samples consisted of two sets of samples. In the first set, the samples contained oxycodone and *S*-ketamine; in the second set, they contained oxycodone and dexmedetomidine.

Microbiological analysis

Absence of antimicrobial activity of the drug solutions was confirmed with the test solutions containing the highest drug concentrations. Two PCA reservoirs containing oxycodone 1 mg/mL+dexmedetomidine 10 µg/mL and two reservoirs containing oxycodone 1 mg/mL+*S*-ketamine 0.75 mg/mL were filled for this evaluation. The technique of membrane filtration was used as described in European Pharmacopoeia Section 2.6. 1 (Ph. Eur. 2.6.1).[13] All the samples were withdrawn from PCA reservoirs with a sterile Luer Lock single-use syringe. In this procedure, at the beginning the membrane is rinsed with a small volume of the sterile solution, followed with the filtration of the sample to be used in the method suitability test. After this, three repeated rinsings of the membrane are done with the sterile solution. Into each of these last rinsings, a small volume of each microbial strain to be tested is added. This test was carried out with six microbial strains: *Aspergillus brasiliensis* (ATCC 16404), *Bacillus spizizenii* (ATCC 6633), *Candida albicans* (ATCC 10231), *Clostridium sporogenes* (ATCC 19404), *Pseudomonas aeruginosa* (ATCC 9027) and *Staphylococcus aureus* (ATCC 6538). The filtered volume was 20 mL per membrane. The growth of anaerobic bacteria was examined with membranes incubated in a thioglycolate medium at 30–35°C. The growth of aerobic bacteria and fungi was examined with membranes incubated in a soybean casein digest medium at 20–25°C. After 5 days of incubation, the turbidity of each separate media containing six different microbial strains (mentioned above) was observed in accordance with the requirements of the Ph. Eur. method suitability test.

Testing for sterility was carried out using the technique of membrane filtration as described in Ph. Eur. 2.6.1.[13] For the sterility testing, sample size was 20 mL both for thioglycolate medium and for soybean casein digest medium. All the samples were withdrawn from PCA reservoirs with a sterile Luer Lock single-use syringe. The growth of anaerobic bacteria was examined with membranes incubated in a thioglycolate medium at 30–35°C. The growth of aerobic bacteria and fungi was examined with membranes incubated in a soybean casein digest medium at 20–25°C. After 14 days of incubation, the turbidity of the media was observed. Twenty-one PCA reservoirs were filled for this assessment, and three parallel PCA reservoirs of each mixture or solution were examined. Sterility samples were aseptically sampled on days 0, 14, 28 and 30. Samples for all microbiological studies were taken and analysed at MetropoliLab (Helsinki, Finland).

Physical stability studies

A total of 42 PCA reservoirs were filled to conduct physicochemical evaluations, with six parallel PCA reservoirs for each drug mixture or oxycodone solution. Sample weight and pH were recorded on days 0, 3, 7, 14, 21, 28 and 30. Each PCA reservoir was weighed before and after each sampling day to indicate the possible loss of solvent. A 5 mL sample was taken for pH measurement with a calibrated pH meter (Mettler Toledo Seven-Compact S220, Greifensee, Switzerland). The pH meter was calibrated before each test with commercially available buffer solutions. Visual control of each PCA reservoir was performed

by observing the samples against a brightly illuminated standard background to determine physical changes in appearance, such as changes in colour, opalescence, precipitation or gas bubble formation.

Osmolality was measured with an automatic osmometer (Automatic Osmometer Model 3900, Advanced Instruments, Norwood, MA, USA). The osmometer was calibrated before each test with a commercially available solution. Osmolality evaluation was conducted on days 0 and 30 at the hospital laboratory of Turku University Hospital. A 2 mL sample was used for osmolality determination. A summary of test schedules is described in online supplemental table 1.

Chemical stability studies

To measure the study samples, we validated an analytical method for the simultaneous determination of oxycodone, *S*-ketamine and dexmedetomidine with reversed-phase high-performance liquid chromatography with ultraviolet detection (HPLC-UV). The analytical method was validated according to US Food and Drug Administration (FDA)[14] and International Conference on Harmonisation (ICH) Q2(R1)[15] guidelines; full validation data are provided in the online supplemental Text. Validation demonstrated acceptable selectivity, carry-over, linearity, accuracy, precision and short-term stability across the relevant concentration ranges for oxycodone, *S*-ketamine and dexmedetomidine.

Quantitation of the analytes was assessed with reversed-phase HPLC-UV. In the validated method no internal standard was used. A sample batch consisted of a blank sample (9 mg/mL (0.9%) sodium chloride solution), eight calibration standards, six quality control samples and a set of study samples. The target concentrations in sample analysis were 1000 µg/mL for oxycodone, 250 µg/mL, 500 µg/mL and 750 µg/mL for *S*-ketamine and 2.5 µg/mL, 5 µg/mL and 10 µg/mL for dexmedetomidine.

The quality requirements of the PCA reservoirs in terms of physicochemical and microbiological stability and the test methods used are presented in table 2.

RESULTS

Microbiological quality

Absence of antimicrobial activity was demonstrated for all tested drug mixtures (oxycodone 1 mg/mL+dexmedetomidine 10 µg/mL, n=2 and oxycodone 1 mg/mL+*S*-ketamine 0.75 mg/mL, n=2) against all of the six reference strains of microbes. The test solutions did not inhibit microbial growth. The results of this microbiological validation indicate that the tested drug mixtures did not interfere with the sterility test results. Thus, the results of the sterility tests can be considered reliable.

All microbiological samples from the 21 PCA reservoirs used for sterility testing were observed to be clear of turbidity over the entire study period. Thus, the studied drug solutions could be considered free of microbial growth and thus sterile. The results indicate that solutions prepared in a European Union Good Manufacturing Practice (GMP) Class B laboratory in a Class A laminar flow hood at Turku University Hospital Pharmacy, containing oxycodone with or without *S*-ketamine or dexmedetomidine diluted in 9 mg/mL (0.9%) sodium chloride solution, remain sterile and free of microbial growth in PCA reservoirs when stored at 2–8°C for at least 28 days and thereafter at room temperature (20–25°C) for 2 days at Turku University Hospital.

Table 2 Quality requirements of patient-controlled analgesia reservoirs for the stability study

Critical quality attribute	Test method	Acceptance criteria
Appearance	Organoleptic study	Clear and colourless solution, no visible particles, precipitation or gas bubble formation
pH of solution	pH meter	4.5–7
Osmolality of solution	Osmometer	Initial ±5%
Concentration of drug substance(s)	Reversed-phase HPLC-UV	90–110% at the end of stability study compared with initial concentration (t=0)
Weight variation	Gravimetric (weighting)	Initial ±5%
Microbiological purity	Membrane filtration	Sterile

Acceptance criteria are based on European Pharmacopoeia (Ph. Eur.) criteria.
HPLC-UV, high-performance liquid chromatography with ultraviolet detection.

Physical stability

All drug solutions were initially clear and colourless and remained unchanged over the study period. No physical changes in appearance, such as visible particles, discolouration, opalescence, precipitation or gas bubble formation, were observed in any test sample. Some loss of weight, up to 0.3% per month, was observed in the drug solutions when stored at 2–8°C for 28 days and thereafter at room temperature (20–25°C) for 2 days (table 3). Loss of solvent vehicle was accelerated with increasing temperature. The small obtained loss of weight did not affect the quality and the patient safety of concentrations of the studied substances. The evaporation of solvent was thus considered insignificant.

The pH of oxycodone solutions slightly increased but storage at room temperature (20–25°C) did not show a significant effect on pH (table 4). The pH of mixtures of oxycodone and dexmedetomidine slightly decreased when PCA reservoirs were stored at 2–8°C and then transferred to room temperature (20–25°C). The pH of mixtures of oxycodone and *S*-ketamine slightly increased when PCA reservoirs were stored at 2–8°C. Storage at room temperature (20–25°C) decreased the pH, which was found to be lower than the initial pH. There were no clinically meaningful differences in the pH values between the samples. During the study period, all pH variations were within the required range of 4.5–7. The measured pH of the PCA reservoirs was always lower than the pKa values of the active substances in them.

The osmolality values of all test solutions slightly increased from the initial state during the study period. The increase in osmolality values in the PCA reservoirs was always less than 1.4%, which can be considered insignificant in terms of physical stability. The measured osmolality values were slightly below the conventional reference range of osmolality of human blood plasma, but the differences between the osmolality values measured in the samples were not clinically meaningful.

Chemical stability studies

The results of the analytical method validation proved that our method is appropriate for the determination of concentrations of oxycodone, *S*-ketamine and dexmedetomidine in PCA drug solutions prepared in sterile 9 mg/mL (0.9%) sodium chloride solution. The assay showed linear responses in the tested concentration ranges of 600–1200 µg/mL for oxycodone, 200–1000 µg/mL for *S*-ketamine and 2–12 µg/mL dexmedetomidine. For validation results see Parts 2, 3 and 4 in online supplementary text and supplementary tables 2,3. Example chromatograms are shown in figure 1.

Table 3 Mean weights of the patient-controlled analgesia reservoirs

Drug solution or mixture	Mean weight (g)*	Weight loss during the study (%)†		
		2–8°C	20–25°C	Total
Oxycodone 1 mg/mL	1635 (1.96)	0.17	0.12	0.29
Oxycodone 1 mg/mL+dexmedetomidine 2.5 µg/mL	163 (0.51)	0.10	0.07	0.17
Oxycodone 1 mg/mL+dexmedetomidine 5 µg/mL	164 (0.62)	0.19	0.09	0.28
Oxycodone 1 mg/mL+dexmedetomidine 10 µg/mL	165 (0.36)	0.17	0.10	0.27
Oxycodone 1 mg/mL+*S*-ketamine 0.25 mg/mL	165 (0.15)	0.21	0.08	0.29
Oxycodone 1 mg/mL+*S*-ketamine 0.50 mg/mL	163 (0.45)	0.15	0.06	0.21
Oxycodone 1 mg/mL+*S*-ketamine 0.75 mg/mL	164 (0.34)	0.06	0.11	0.17

Results are shown as mean (SD). n=6.
*Results are presented as mean (SD), n=6.
†Samples were first stored at 2–8°C for 28 days, after which the reservoirs were transferred to 20–25°C for an additional 2 days.

Oxycodone, *S*-ketamine and dexmedetomidine were found to be stable in the vehicle at room temperature at 20–25°C in the laboratory for at least 48 hours and in the autosampler (+20°C) for 24 hours. Mean accuracies of six stability samples were between 95% and 105% compared with the original concentrations.

The chemical stability results are summarised in table 5 and complete concentration data for all sampling days are presented in online supplemental tables 4,5. Relative concentrations of oxycodone, *S*-ketamine and dexmedetomidine remained within ±5% of the initial concentrations throughout the study period in all PCA reservoirs. These results fulfil the predefined acceptance criteria for chemical stability (table 2).

DISCUSSION

The specific aims defined for this stability study were achieved. We established that the employed aseptic working method for the preparation of PCA drug solutions was appropriate. Microbiological stability of a PCA solution prepared by a hospital pharmacy can be achieved by following the principles defined in the EU GMP guidelines. An HPLC method for the chemical stability testing of oxycodone, *S*-ketamine and dexmedetomidine was successfully developed. The HPLC method was suitable and sufficiently reliable for quantitative concentration analysis of oxycodone and *S*-ketamine or dexmedetomidine in a mixture. Oxycodone was found to be physically compatible and chemically stable in mixtures with *S*-ketamine and dexmedetomidine in PCA reservoirs prepared for clinical use.[16]

The absence of antimicrobial activity of oxycodone solutions diluted (1 mg/mL) in 9 mg/mL (0.9%) sodium chloride solution has been previously documented.[17] The results of our microbiological studies support the conclusion that oxycodone, *S*-ketamine and dexmedetomidine had no antimicrobial activity that could have interfered with the sterility testing. The results of the microbiological validation indicate that the drug mixtures, at the investigated concentrations, did not interfere with the sterility test results. Thus, the results of the sterility tests can be considered reliable.

Based on the results obtained, the expiration date of the studied drug solution and mixtures in PCA reservoirs can be extended to 28 days when stored in a refrigerator (2–8°C). Thereafter, the PCA reservoirs can be used by patients for clinical pain management for 2 days. Some loss of weight, up to 0.3% per month, was observed in the drug solution mixtures during the study period. Loss of solvent vehicle occurred during storage, and evaporative loss increased at higher temperatures, but this did not have clinically meaningful effects on the concentrations of the studied substances.

The extent of solvent evaporation was considered insignificant. Similar results of evaporation of solvent have been reported previously in stability studies of PCA reservoirs. A previous study reported loss of solvent of up to 1% per month for fentanyl and sufentanil diluted in 9 mg/mL (0.9%) sodium chloride solution in portable infusion pumps when stored at 4°C or at room temperature (25°C).[18] Amri *et al*[17] reported some loss of weight, up to 0.6% per month, for 1 mg/mL oxycodone solutions diluted in 9 mg/mL (0.9%) sodium chloride solution in portable infusion pumps. In their study, different types of infusion pumps were used (CADD and Rythmic reservoirs), and they were stored at room temperature (15–25°C). Regardless of storage conditions, no visible particles, discolouration, opalescence, precipitation or gas bubble formation were observed in either study.

Storage conditions had no significant impact on the chemical stability of the contents of the PCA reservoirs. According to the physical stability results, the evaporation of solvent during the study period may be related to the observed increase of drug concentrations. No degradation products or impurities were found during the physical stability study period. Possible impurities might be those described in the European Pharmacopoeia for oxycodone (specified impurities A, B, C, D, E and F) and for *S*-ketamine (specified impurities A, B, C and D).[19] A possible impurity for dexmedetomidine might be levomedetomidine.

Similar results for the chemical stability of oxycodone diluted in 9 mg/mL (0.9%) sodium chloride solution have been reported previously. Turnbull *et al*[20] reported that 5 mg/mL and 50 mg/

Table 4 Mean pH values of patient-controlled analgesia reservoirs.

Drug solution or mixture	Initial pH*	pH at 2–8°C	pH at 20–25°C
Oxycodone 1 mg/mL	5.61 (0.09)†	5.87 (0.18)	5.86 (0.05)
Oxycodone 1 mg/mL+dexmedetomidine 2.5 µg/mL	6.11 (0.08)	5.94 (0.06)	5.84 (0.03)
Oxycodone 1 mg/mL+dexmedetomidine 5 µg/mL	6.05 (0.04)	5.92 (0.09)	5.81 (0.05)
Oxycodone 1 mg/mL+dexmedetomidine 10 µg/mL	6.00 (0.05)	5.94 (0.09)	5.89 (0.05)
Oxycodone 1 mg/mL+*S*-ketamine 0.25 mg/mL	5.34 (0.11)	5.44 (0.06)	5.22 (0.02)
Oxycodone 1 mg/mL+*S*-ketamine 0.50 mg/mL	5.11 (0.08)	5.23 (0.06)	5.00 (0.02)
Oxycodone 1 mg/mL+*S*-ketamine 0.75 mg/mL	5.04 (0.01)	5.10 (0.08)	4.90 (0.05)

*Initial refers to day 0 of the study, 2–8°C to day 28, and 20–25°C to day 30 after an additional 2 days at room temperature.
†Results are presented as mean (SD), n=6.

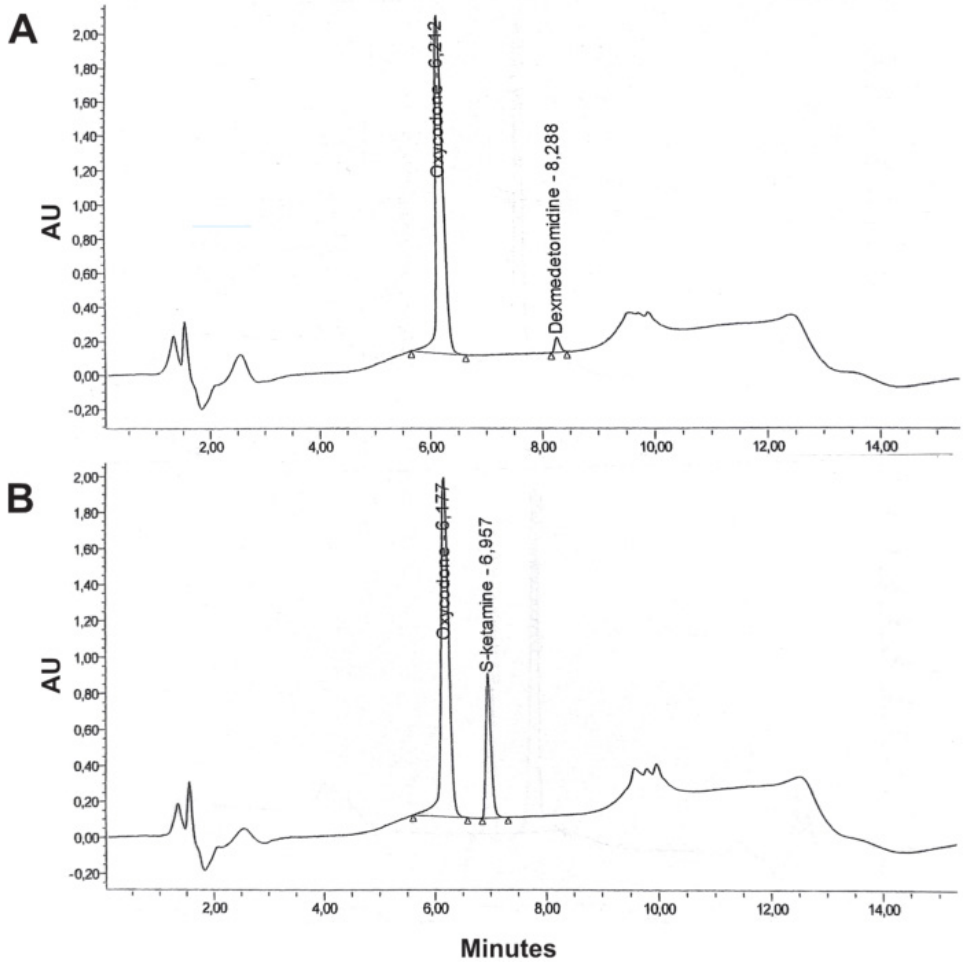

Figure 1 Chromatograms of two quality control samples containing (A) oxycodone 1 mg/mL and *S*-ketamine 0.5 mg/mL and (B) oxycodone 1 mg/mL and dexmedetomidine 5.0 µg/mL. AU, absorbance unit.

mL oxycodone hydrochloride in 9 mg/mL (0.9%) sodium chloride solution retained more than 95% of the initial drug concentrations during 35 days of storage in polyvinyl chloride (PVC) minibags at 4°C and 35°C. Only small changes in oxycodone concentrations were also previously reported during 28-day storage of 1 mg/mL oxycodone in 9 mg/mL (0.9%) sodium chloride solution in portable infusion pumps.[17] In that study, two different types of infusion pumps (CADD and Rythmic reservoirs) were kept at room temperature (15–25°C). Oxycodone concentrations decreased 1.4% in CADD reservoirs and increased 1.5% in Rythmic reservoirs.[17] In the same study, oxycodone concentrations decreased 3.9% in Rythmic reservoirs protected from light, but no impact on product stability was noted. Because of the use of different infusion pumps, the previous results are not fully comparable with our setting. For example, evaporation of water may vary between different infusion pumps and their reservoirs.

Table 5 Relative concentrations of oxycodone, *S*-ketamine and dexmedetomidine in patient-controlled analgesia reservoirs after 30 days of storage

Mixture	Analyte	Relative concentration (% of day 0 result) Mean (SD)
Oxycodone 1 mg/mL	Oxycodone	101.15 (0.40)
Oxycodone 1 mg/mL+*S*-ketamine 0.25 mg/mL	Oxycodone	102.01 (1.27)
	S-Ketamine	101.53 (0.50)
Oxycodone 1 mg/mL+*S*-ketamine 0.50 mg/mL	Oxycodone	101.58 (0.41)
	S-Ketamine	99.59 (0.44)
Oxycodone 1 mg/mL+*S*-ketamine 0.75 mg/mL	Oxycodone	100.18 (0.31)
	S-Ketamine	95.80 (0.48)
Oxycodone 1 mg/mL+dexmedetomidine 2.5 µg/mL	Oxycodone	102.02 (0.63)
	Dexmedetomidine	96.51 (0.95)
Oxycodone 1 mg/mL+dexmedetomidine 5 µg/mL	Oxycodone	104.08 (0.73
	Dexmedetomidine	98.72 (1.22)
Oxycodone 1 mg/mL+dexmedetomidine 10 µg/mL	Oxycodone	104.64 (0.66)
	Dexmedetomidine	101.42 (1.10)

The stability of oxycodone solutions in syringes used for long-duration infusions has been evaluated previously.[17 20] A previous report stated that oxycodone hydrochloride prepared in sterile water retained more than 95% of the original concentration during 35 days of storage at 4°C and 35°C.[17] The same result was observed with oxycodone solutions diluted with different solvents.[20] More relevant to the current study, a long-term stability study of oxycodone solutions stored in a PCA reservoir over 28 days showed no significant changes in pH, weight or osmolality.[17]

Similar results have been reported for ketamine and dexmedetomidine. Daouphars *et al*[21] reported that *S*-ketamine (0.1–40 mg/mL) combined with oxycodone (0.4–10 mg/mL) was

chemically stable for 7 days at room temperature (23°C) when diluted in 9 mg/mL (0.9%) sodium chloride solution and packaged in polypropylene syringes or PVC bags. All formulations maintained more than 95% of their initial drug concentrations over the study period. Chromatograms showed no detectable degradation products for any analyte. Solutions of ketamine combined with morphine were physicochemically stable at 5°C and 23°C for 91 days when diluted with 9 mg/mL (0.9%) sodium chloride solution.[22] Exposure to light had no impact on the stability of these drugs, as their concentrations remained above 98% of the original concentration under both storage conditions.[22] Mixtures of tramadol with ketamine in 9 mg/mL (0.9%) sodium chloride solution prepared for PCA delivery systems were stable for 14 days when stored at 4°C and 25°C.[23]

The stability of four different concentrations of dexmedetomidine hydrochloride (4, 8, 12 and 20 µg/mL) have been tested in PVC bags containing 9 mg/mL (0.9%) sodium chloride solution.[24] Solutions remained stable at room temperature at 20–25°C, over the 48-hour testing period, and only small pH decreases were seen with increasing dexmedetomidine concentrations.[24]

A key limitation of the present study is that forced degradation experiments were not performed. Consequently, the stability-indicating capability of the analytical method cannot be fully confirmed, as the method's ability to separate potential degradation products from the parent compounds was not systematically verified using stress conditions. Although no additional chromatographic peaks suggesting degradation were observed during the study period, the absence of forced degradation data means that co-eluting degradation products cannot be definitively excluded. Despite this limitation, the results provide clinically relevant preliminary evidence on the physicochemical stability of the investigated admixtures under hospital pharmacy conditions. The analytical method was validated for quantification of the parent compounds, and chromatographic profiles of stored samples remained comparable to freshly prepared solutions throughout the study period. Furthermore, the study conditions, including drug concentrations, diluents and storage parameters, were selected to reflect routine clinical practice. Therefore, while the findings should be interpreted with caution and not considered definitive proof of stability-indicating performance, they support the short-term usability of these admixtures in clinical settings. Future studies incorporating forced degradation experiments are warranted to confirm the stability-indicating properties of the method.

These findings have direct implications for hospital pharmacy practice. The present findings suggesting that oxycodone PCA formulations containing *S*-ketamine or dexmedetomidine remain chemically stable and sterile for 28 days at 2–8°C (plus 2 days at room temperature at 20–25°C) may support the use of extended beyond-use dates and enable centralised batch compounding. This can reduce aseptic workload, improve utilisation of cleanroom capacity, and decrease material and drug waste. The validated analytical method and consistent sterility results provide evidence-based assurance of product quality throughout the storage period. As demand for opioid–adjuvant PCA combinations increases, such stability data are essential for safe, efficient and sustainable provision of compounded sterile preparations in hospital pharmacies.

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Contributors PV, KT and TIS conceived the study. KT and TIS designed the study protocol. PV was responsible for preparation of the patient-controlled analgesia solutions and conducted the experimental work. SS, KP and MS performed the analytical method development and validation. PV, SM, SS, PU, KT and TIS analysed and interpreted the data. TIS drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission. TIS is the guarantor of this work and accepts full responsibility for the integrity of the data and the accuracy of the analysis. During the preparation of this article, the authors used ChatGPT to improve language and readability. After using this tool/service, the authors reviewed and edited the contents as needed and take full responsibility for the contents of the publication.

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