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Butorphanol and Ketamine Combined in Infusion Solutions for Patient-Controlled Analgesia Administration: A Long-Term Stability Study

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Background: Ketamine in subanesthetic dose added to butorphanol has been reported to give superior pain control when used for intravenous patient-controlled analgesia (PCA) after surgery. However, this admixture is not available commercially and stability data applicable to hospital practice are limited.

Material/Methods: The butorphanol-ketamine admixtures were prepared in polyolefin bags and stored in the dark at 4°C, 25°C, or 37°C for 15 days. The initial concentrations were 50–150 microgram/ml for butorphanol and 1–4 mg/ml for ketamine, respectively. The stabilities were determined by visual inspection, pH measurement, and high-pressure liquid chromatography (HPLC) assay of drug concentrations.

Results: Over the 15 days, all solutions were clear in appearance, and no color change or precipitation was observed among the three temperatures. The percentages of initial concentration of each drug were over 95% during the study period, and the pH value did not change significantly.

Conclusions: The results indicate that the drug mixtures of butorphanol and ketamine in 0.9% sodium chloride injection were stable for 15 days when stored in polyolefin bags at 4°C, 25°C, or 37°C.

MeSH Keywords: **Analgesia, Patient-Controlled • Butorphanol • Chromatography • Drug Stability • Ketamine • Pain, Postoperative**

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Background

An effective postoperative pain management regimen is vital to patient recovery after surgery. Multi-modal analgesia, using different classes of analgesics, is the currently recommended method to obtain this goal [1,2]. Of the multi-modal approach, adding an adjunct to an opioid-based intravenous (i.v.) patient-controlled analgesia (PCA) as a convenient regimen for moderately severe pain control is popularity used worldwide in clinical practice [3]. Various adjunct drugs, such as nonsteroidal anti-inflammatory drugs [4,5], N-methyl-D-aspartate (NMDA) antagonists [6], antiemetic [7], alpha-2 adrenergic agonists [8], and glucocorticoids [9] have been used in these multi-modal protocols.

Butorphanol tartrate, a synthetic opioid, is a μ -opioid antagonist and a κ -receptor agonist [10]. Similar to other opioid analgesics, the common adverse effects such as nausea and/or vomiting, somnolence, and dizziness are considerations with butorphanol [11]. Continuous PCA intravenous of butorphanol has been proposed since the 1980s [12], but may increase the incidence of postoperative nausea and vomiting (PONV), which leads to the discontinuance of its administration [13]. To prevent PONV, adjuvant medications are widely used. Ketamine hydrochloride, an analgesic/sedative, is a non-competitive antagonist at the NMDA receptor [14]. Subanesthetic doses of ketamine prevent the induction of central sensitization, development of acute opioid tolerance, and hyperalgesia [15]. A large number of clinical trials [16–20] and systemic reviews [21–23] have evaluated the efficacy of ketamine as an adjuvant to opioids in i.v. PCA for postoperative pain; some of those studies demonstrated an opioid-sparing effect and subsequent reduction in the incidence of PONV. In addition, in a study comparing PCA with a combination of butorphanol and low-dose ketamine with butorphanol alone after surgery, pain scores were lower in the patients who received both drugs [16].

However, there are no commercially available drug mixtures, and they must be prepared in hospital pharmacy departments for clinical use. Mixing two or more drugs together in infusion solutions can lead to physical and/or chemical changes, which may result in a variation in therapeutic properties and unknown side effects [24,25]. To the best of our knowledge, few data are available about compatibility and stability of butorphanol in combination with other drugs [26–30] and there are no reports about mixture with ketamine. Thus, to provide background information on the storage of a **butorphanol-ketamine** mixture, the objective of the current study was to evaluate the stability of butorphanol-ketamine solutions at 3 different concentration combinations, which were prepared in 0.9% sodium chloride and stored for a period of up to 15 days at 4°C, 25°C, and 37°C.

Material and Methods

Chemicals and reagents

The reference standards of butorphanol tartrate and ketamine hydrochloride were purchased from the National Institute for the Pharmaceutical and Biological Products (Beijing, China) and stored at 4°C. Butorphanol tartrate injection (1 mg/1 mL, lot number 121225) was obtained from Hengrui Medicine Co., Ltd. (Jiangsu, China). Ketamine hydrochloride injection (100 mg/2 mL, lot number 130202) was purchased from Qilu pharmaceutical Co., Ltd. (Shandong, China). Sodium chloride injection 0.9 mg·mL⁻¹ was supplied by Kelun Pharmaceutical Co., Ltd. (Sichuang, China). HPLC-grade acetonitrile and potassium dihydrogen phosphate KH₂PO₄ were purchased from Wuhan Analytical reagent company (Wuhan, China). Ultrapure water was purified using a Milli-Q system (Millipore, Bedford, MA, USA).

HPLC equipment and chromatographic conditions

The Dionex HPLC system consisted of a UltiMate 3000 quaternary gradient pump, an ASI-100 auto sampler, a TCC-100 thermostat column oven, an ultraviolet detector (DAD), and a data system (Chromeleon® version 6.80). HPLC separation was performed on a Zorbax SB-C₁₈ analytical column (150×4.6 mm, 5.0 μ m). The mobile phase consisted of 0.05 mol/L KH₂PO₄ and acetonitrile in the proportion of 70: 30 (v/v), with a flow rate of 1.0 ml/min. The wavelength was set at 280 nm for butorphanol and 268 nm for ketamine. The column temperature was kept ambient and injection volume was 20 μ L.

Preparation of stock and working solutions

The standard stock solutions were prepared by dissolving 12.5 mg of butorphanol tartrate and 52.0 mg ketamine hydrochloride in 10 ml 0.9% sodium chloride infusion solution to yield a nominal concentration of 1.25 mg/ml and 5.20 mg/ml, respectively. The solutions were kept at –20°C until use. Fresh working standard solutions were prepared by diluting the stock solution with 0.9% sodium chloride to the required concentrations before use.

Validation of the method

Validation of the method was performed according to the guidelines defined in CDERs reviewer guidance on Validation of Chromatographic Methods [31,32]. Linearity was measured by constructing a six-point calibration curve of butorphanol tartrate and ketamine hydrochloride in a range 2.50–250.0 μ g/mL and 0.078–1.56 mg/mL, respectively. Linear regression was calculated by the peak area vs. concentration curves. Assays of control solutions at three different levels of concentration of butorphanol tartrate (10.0, 20.0, and 30.0 μ g/mL) and

Table 1. Admixtures of butorphanol tartrate and ketamine hydrochloride.

Drug mixture	Butorphanol tartrate		Ketamine hydrochloride	
	C (mg/ml)	Dose (mg/day)	C (mg/ml)	Dose (mg/day)
1	0.05	2.5	1.00	50
2	0.05	2.5	2.00	100
3	0.05	2.5	4.00	200
4	0.10	5.0	1.00	50
5	0.10	5.0	2.00	100
6	0.10	5.0	4.00	200
7	0.15	7.5	1.00	50
8	0.15	7.5	2.00	100
9	0.15	7.5	4.00	200

ketamine hydrochloride (208.0, 416.0, and 832.0 µg/mL) were undertaken to calculate the accuracy and intra-day and inter-day precision. Accuracy and intra-day precision were estimated by means of the recovery value and relative standard deviation (RSD,%) calculated from three control solutions with five determinations per concentration at the same day. Inter-day precision (5 days) was also estimated as the RSD calculated from five replicate mixture samples prepared in the same way. The limit of detection (LOD) and limit of quantification (LOQ) for butorphanol tartrate and ketamine hydrochloride standards were determined based on the standards/baseline signal-to-noise (S/N) ratio. Dilutions and injections of two standards were then made until an HPLC chromatograph showed that the two peak height reached an S/N of approximately 10:1 and 3:1 for LOQ and LOD solutions, respectively.

Stability indication

The stability-indicating capability of the chromatographic method was assessed using partially decomposed solutions of drug. The butorphanol tartrate and ketamine hydrochloride mixture degraded by heating at 60°C for 5 hours under acidic (0.1 mol/L hydrochloric acid), basic (0.1 mol/L sodium hydroxide) and 3% hydrogen peroxide (H₂O₂) conditions was assayed to confirm separation of the parent molecule from its degradation products. The chromatogram obtained from the degraded solution was compared with a chromatogram obtained from the standard solutions to determine whether or not any degradant peaks were produced, which would interfere with the quantification of butorphanol tartrate and ketamine hydrochloride.

Preparation of admixtures

The final dose and concentration of each drug in the study were chosen by taking into consideration those more frequently used

for postoperative pain [16–20]. The doses assayed were 2.5, 5.0, and 7.5 mg/day for butorphanol tartrate and 50, 100, and 200 mg/day for ketamine hydrochloride. According to this, nine different butorphanol tartrate-ketamine hydrochloride solutions were prepared in 0.9% sodium chloride injection (Table 1). The initial concentration ranges were 0.05–0.15 mg/ml for butorphanol tartrate and 1.0–4.0 mg/ml for ketamine hydrochloride.

Nine samples of each solution were prepared, which enabled triplicate syringes to be stored in the dark at 4°C, 25°C, and 37°C. The mixtures were made up in volumes reflecting those used in 2-day infusion pumps (100 ml) and prepared by transferring the contents of the corresponding drug ampoules used in each mixture, and then adding 0.9% sodium chloride injection to give 100 ml. All the solutions were prepared in commercial polyolefin bags under aseptic conditions in laminar flow hoods and using sterile drug solutions.

Stability study of the analgesic mixtures

Following American Society of Health-System Pharmacists guidelines, samples were removed from each admixture for analysis of appearance, pH, and drug concentration on days 0, 1, 2, 3, 5, 7, 10, and 15. At the specified times, the solutions were examined for the development of color, cloudiness, precipitation, and gas production. These macroscopic determinations of the samples were observed against light and dark backgrounds. Moreover, at time 0 and 15 days, the pH of each mixture was measured by using a digital phs-3c pH meter (Leici Instrument Co., Shanghai, China). Finally, all samples were then frozen at –20°C until analysis. Samples were allowed to reach room temperature and diluted 4-fold in 0.9% sodium chloride infusion solution before injection into a HPLC system. Each sample was assayed in triplicate by HPLC.

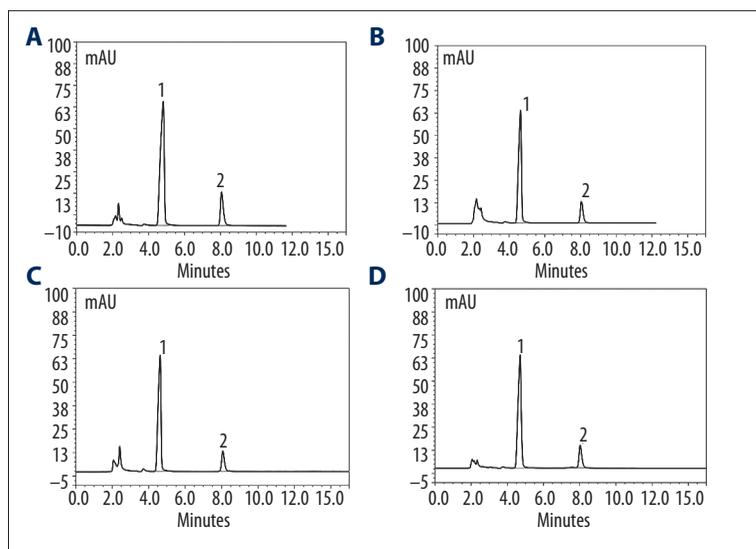


Figure 1. Chromatograms obtained from the drug mixtures degradation testing. Key to plots: (A) samples were freshly prepared; (B) samples were exposed to 0.1 mol/L hydrochloric acid at 60°C for five hours; (C) samples were exposed to 0.1 mol/L sodium hydroxide at 60°C for five hours; (D) samples were exposed to 3% hydrogen peroxide at 60°C for five hours. Retention times were 4.8 minutes for ketamine hydrochloride (peak 1) and 8.1 minutes for butorphanol tartrate (peak 2). The other peaks were for degradation products.

Analysis of data

Data are expressed as the mean \pm standard deviation (SD). At time zero, the initial concentration of both drugs was designated as 100.0%; all subsequent concentrations were expressed as a percentage of the initial concentration. The admixtures were considered chemically stable if they retained 90% of the initial concentrations. The changes with time of the concentrations of the drugs in solution were analyzed using one-factor ANOVA. A P-value of less than 0.05 was considered to be significant.

Results

Validation of the HPLC method

Drug concentrations were determined by using a stability indicating HPLC assay. For butorphanol tartrate, a good linear response was found between the peak area vs. concentration with a correlation coefficient (r) better than 0.9994 ($y=0.0695x+0.1286$). For ketamine hydrochloride, the linear regression analysis of the peak area of the drug concentration yielded a correlation coefficient (r) better than 0.9992 ($y=0.0342x+0.3106$). Chromatograms of the degradation samples were shown in Figure 1, demonstrating that the decomposition products were baseline separated from analytes and none would interfere with the quantification of butorphanol tartrate and ketamine hydrochloride. The intra-day and inter-day variations RSD% at three concentrations were all less than 2.5% for both drugs, with the recoveries obtained also being close to 100%. The LOD was found to be 0.38 $\mu\text{g/mL}$ for butorphanol tartrate and 0.21 $\mu\text{g/mL}$ for ketamine hydrochloride. The LOQ was found to be 1.25 $\mu\text{g/mL}$ for butorphanol tartrate and 0.73 $\mu\text{g/mL}$ for ketamine hydrochloride. These

results indicate that the method provides adequate accuracy and precision for quality control of butorphanol and ketamine in sodium chloride (0.9%).

Stability of the analgesic mixtures

All the mixtures assayed could be considered as physically compatible since no evidence of incompatibility (precipitation, turbidity, color change, opacity or gas production) were observed. Tables 2–4 show the percentages of dose remaining of butorphanol tartrate and ketamine hydrochloride in the admixtures when the tests were carried out at 4°C, 25°C, and 37°C, respectively. The percentages of butorphanol tartrate and ketamine hydrochloride remaining in the drug mixtures were higher than 96.0% with non-statistically significant differences found between temperatures and sampling times ($p>0.05$). No degradation products of butorphanol and ketamine were detected in any of the admixtures. Over the 15 days, the pH value was close to pH 5 and changes were within 0.1 units of the initial pH for all drug mixtures

Discussion

For PCA, drugs with different analgesics are commonly combined to provide more effective analgesia and reduce the incidence of unknown side effects compared with a single drug [3]. Li et al. [16] and Zhao et al. [17] have reported that butorphanol with subanesthetic dose ketamine via PCA pump can be used with good effect and less side effects for analgesia and sedation. Furthermore, in our institution, solutions containing both butorphanol and ketamine have been sometimes used for postoperative patients. However, no information is available about the chemical stability of this analgesic mixture. In many cases, combinations of drugs are administered

Table 2. Mean (SD) concentrations of butorphanol tartrate and ketamine hydrochloride in 0.9% sodium chloride polyolefin bags stored at 4°C (n=3).

Time (days)	Admixture								
	1	2	3	4	5	6	7	8	9
	Butorphanol								
1	100.4±0.7	99.9±0.1	100.4±0.6	99.7±0.2	100.3±0.5	100.6±0.5	101.5±0.2	101.2±0.8	102.0±0.5
2	102.0±0.3	100.8±0.3	100.1±0.6	100.5±0.2	101.5±0.2	98.7±2.4	100.0±0.6	101.3±2.0	100.5±1.2
3	100.0±0.1	101.2±0.1	99.9±0.9	100.7±0.7	100.6±0.3	100.4±1.1	102.3±1.6	99.9±0.7	102.1±2.6
5	99.7±0.2	100.3±1.1	103.1±1.0	101.4±1.6	101.4±0.2	102.0±1.6	100.4±0.1	98.9±1.1	100.7±0.2
7	100.5±0.8	101.2±1.1	100.7±0.8	100.8±0.2	101.6±1.4	100.5±0.4	100.3±0.3	100.3±1.0	101.0±1.0
10	101.4±1.1	99.9±1.6	101.2±0.8	98.8±0.1	100.4±0.7	102.2±0.9	101.2±1.2	102.0±1.5	99.8±0.1
15	99.8±0.5	101.1±0.8	100.3±1.2	101.0±2.1	101.2±1.0	101.2±1.0	99.9±0.3	101.5±0.9	100.2±0.3
	Ketamine								
1	99.7±1.0	100.3±0.8	102.0±0.4	100.2±0.1	99.2±0.3	99.9±0.1	100.6±0.8	101.5±0.7	100.7±1.9
2	101.1±0.7	101.8±1.4	100.3±1.4	99.8±0.3	100.6±0.2	101.3±1.5	102.3±1.7	101.3±0.4	99.9±0.5
3	102.2±0.9	99.3±1.1	101.2±0.2	98.6±0.4	97.5±0.6	98.7±0.2	99.7±0.8	100.1±0.7	101.3±1.0
5	100.3±0.2	102.1±1.5	99.7±0.7	100.3±0.9	98.7±2.1	99.0±0.1	99.3±1.2	99.8±0.6	102.4±2.1
7	99.3±0.5	98.7±0.6	99.4±0.5	97.8±1.0	98.3±1.1	99.2±0.2	99.6±0.3	99.3±0.2	100.0±0.6
10	99.5±1.3	99.7±0.8	100.2±0.5	98.2±0.6	98.6±0.9	98.0±0.5	98.5±0.3	97.9±0.2	99.3±0.4
15	99.6±1.1	99.3±0.2	99.3±1.1	97.7±1.3	99.2±0.4	99.4±1.0	98.3±0.7	98.7±0.3	98.1±0.5

Table 3. Mean (SD) concentrations of butorphanol tartrate and ketamine hydrochloride in 0.9% sodium chloride polyolefin bags stored at 25°C (n=3).

Time (days)	Admixture								
	1	2	3	4	5	6	7	8	9
	Butorphanol								
1	98.3±1.0	100.9±1.2	99.6±0.9	101.1±0.7	101.5±0.5	99.6±1.0	102.2±1.6	99.7±0.6	99.7±0.7
2	99.5±0.8	101.4±1.4	100.5±0.1	102.6±1.5	100.0±0.6	98.1±0.2	100.7±0.7	102.0±1.8	98.6±0.2
3	100.2±1.1	99.6±0.5	97.8±2.0	99.2±1.0	100.8±0.2	103.4±1.1	99.6±0.2	100.9±1.2	100.0±1.0
5	101.1±0.7	99.8±1.5	99.6±1.0	99.8±0.2	101.1±1.1	100.8±2.7	102.5±1.3	102.2±0.6	99.5±1.4
7	99.9±0.1	100.6±0.3	100.0±0.7	99.5±0.4	99.0±0.3	99.9±0.4	100.4±0.4	99.8±0.8	99.5±0.1
10	101.9±0.9	98.4±0.2	101.7±1.1	98.9±0.3	98.3±1.2	98.5±1.5	101.7±0.5	98.4±1.9	99.4±2.2
15	100.2±0.6	100.7±0.3	99.6±0.2	102.3±1.6	100.8±0.8	101.1±0.6	98.7±0.2	100.9±0.1	101.1±1.3
	Ketamine								
1	101.2±0.1	100.2±0.4	98.7±0.1	99.5±0.1	100.0±0.6	99.3±1.5	100.3±2.4	98.6±1.1	99.7±0.8
2	99.7±0.5	99.9±1.2	100.0±0.8	100.6±1.2	99.7±0.5	99.3±2.0	99.7±1.8	99.1±2.3	98.6±1.2
3	100.1±0.3	99.6±0.2	97.7±1.8	98.8±0.1	103.2±2.6	98.5±0.4	98.6±0.2	100.0±0.1	98.2±1.0
5	98.9±0.2	99.0±0.1	99.7±0.5	99.1±0.1	100.7±0.2	97.4±1.3	102.0±1.1	98.1±1.7	99.2±0.1
7	99.5±0.2	98.4±0.1	99.4±0.2	97.2±0.2	98.3±0.1	97.0±0.4	98.6±0.7	98.8±0.4	97.9±0.9
10	97.2±1.0	99.3±0.4	98.9±0.3	98.8±0.2	96.5±0.3	97.6±0.2	98.2±0.2	98.4±0.2	98.9±1.1
15	97.6±0.6	98.3±1.3	97.5±0.1	98.2±1.1	98.3±0.7	98.9±0.1	97.5±0.6	98.3±0.5	99.0±0.3

Table 4. Mean (SD) concentrations of butorphanol tartrate and ketamine hydrochloride in 0.9% sodium chloride polyolefin bags stored at 37°C (n=3).

Time (days)	Admixture								
	1	2	3	4	5	6	7	8	9
Butorphanol									
1	99.7±1.9	101.4±2.0	98.7±0.2	98.2±0.9	99.8±1.6	101.3±1.7	100.8±0.2	102.6±1.0	101.8±1.6
2	102.3±0.2	98.5±0.8	100.8±0.4	102.1±1.1	100.2±0.2	99.6±0.1	99.4±0.7	100.3±0.3	100.1±0.5
3	99.6±0.1	98.7±1.5	102.1±2.7	99.7±1.0	99.3±0.2	102.2±1.4	102.4±0.8	98.0±0.2	98.4±0.2
5	100.4±0.5	99.1±0.7	101.0±1.6	103.1±1.8	100.5±0.1	100.4±0.8	99.0±0.1	98.9±2.0	100.0±0.2
7	98.4±1.5	102.5±1.8	98.2±0.8	99.4±0.5	99.0±0.5	103.3±1.9	100.5±0.1	101.6±1.1	97.5±1.0
10	100.9±0.6	100.7±0.5	97.5±1.3	98.3±0.2	98.4±0.2	99.6±0.8	97.6±0.5	100.8±0.6	99.2±0.4
15	100.4±0.1	98.2±0.2	99.1±0.5	101.3±1.3	100.1±0.2	101.6±0.4	98.1±1.0	98.9±0.1	102.2±2.3
Ketamine									
1	101.5±1.1	100.4±0.9	98.6±0.1	100.5±0.0	101.9±0.8	99.3±0.2	99.9±0.4	99.1±1.3	101.4±1.6
2	102.1±1.7	99.2±0.5	100.6±0.1	101.3±0.8	102.2±1.5	99.9±0.5	101.7±1.0	102.5±2.3	98.3±0.2
3	101.6±0.9	99.7±0.2	97.2±0.8	101.8±0.4	98.7±2.1	100.4±1.6	99.2±0.1	99.3±0.5	100.5±0.2
5	98.5±0.2	99.3±0.2	102.4±1.4	98.6±0.8	100.3±0.9	98.7±0.1	101.4±0.3	98.7±0.7	99.0±1.0
7	101.8±1.0	98.4±0.1	100.3±1.9	97.9±0.1	99.6±0.2	97.8±0.1	100.8±0.6	99.0±0.6	100.1±0.3
10	97.3±0.5	99.6±0.2	98.6±0.2	99.2±0.2	99.7±0.2	100.3±0.7	99.8±1.5	96.7±0.3	99.2±0.7
15	97.5±0.3	97.9±0.1	99.3±1.5	99.4±1.1	98.9±0.4	98.8±1.2	99.4±0.5	99.2±0.9	98.5±1.4

together, resulting in the possibility of drug incompatibility or loss of stability. This may cause drug precipitation or crystallization, resulting in blockage of the cannula, skin irritation, and poor absorption or loss of potency [33]. Previous studies have demonstrated that these problems may occur when butorphanol is combined with lornoxicam [28]. The precipitation of lornoxicam could be attributed to the formation of lornoxicam, which is a weak acid and has a low solubility in the acidic pH environment. In our study, no precipitation was observed, and there was no modification of the chromatographic peaks observed when butorphanol tartrate was combined in solution with ketamine hydrochloride.

The previous stability and compatibility tests of ketamine hydrochloride single or combined with other drugs in solution have demonstrated that ketamine hydrochloride is a very stable drug. Ketamine hydrochloride was found to be compatible when diluted with water or 0.9% sodium chloride injection, packaging in glass vials, or polypropylene syringes at room temperature [34–36]. The compatibility and stability studies also reported that most of the tested drugs, such as morphine [37–40], hydromorphone [41,42], fentanyl citrate [43], and dexamethasone sodium phosphate [44], were stable and compatible in the presence of ketamine hydrochloride. Unfortunately, no published information is available on the compatibility and stability of butorphanol in combination with ketamine in PCA

solution. Therefore, the aim of this study was to address this lack of information.

The present study has direct relevance to clinical practice. In this stability study, the concentrations of butorphanol tartrate and ketamine hydrochloride chosen reflect the use of the combinations by specialist analgesic treatment teams and clinical research, [16–23] to ensure that the results will have clinical utility.

When mixing drugs taken from ampoules of sterile solutions, there is also the potential issue of bacterial contamination. In this study, we have only examined physicochemical stability without taking into consideration microbial contamination. In clinical practice we should follow the USP/NF Chapter 797 [45]. In this regulation, the preparation belongs to be low-risk compounding sterile product. To ensure the security, the preparation should be used beyond the date at room temperature for 48 hours or at refrigerated temperatures for 14 days on the basis of USP specifications.

Conclusions

In the present study, a reliable analytical HPLC method for the simultaneous determination of butorphanol tartrate and ketamine

hydrochloride in analgesic mixture samples was been successfully developed. Next, the method was used to study the stability of the drug mixture at the usual concentration levels used in PCA. The results of the stability study showed that mixtures of butorphanol tartrate (50–150 microgram/ml) and ketamine hydrochloride (1–4 mg/ml) in 0.9% sodium chloride and stored in

polyolefin bags for 15 days were chemically stable and physically compatible in the different conservation conditions studied.

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Competing interests

None.

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