

# Stability of Butorphanol–Tropisetron Mixtures in 0.9% Sodium Chloride Injection for Patient-Controlled Analgesia Use

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Tropisetron is an adjuvant for butorphanol used in intravenous patient-controlled analgesia (PCA) and has been reported to provide superior pain control. It is efficacious in reducing the incidence of postoperative nausea and vomiting. However, this admixture is not available commercially and stability data applicable to hospital practice are limited. This study aimed to describe the drug compounding and evaluates the long-term (up to 14 days) stability of butorphanol and tropisetron in 0.9% sodium chloride injection for PCA use.

In this study, commercial solutions of butorphanol tartrate and tropisetron hydrochloride were combined and further diluted with 0.9% sodium chloride injection to final concentrations of butorphanol tartrate 0.08 mg/mL and tropisetron hydrochloride 0.05 mg/mL. The polyolefin bags and glass bottles were stored at 4°C and 25°C for up to 14 days. The drug stabilities were determined by visual inspection, pH measurement, and high-pressure liquid chromatography assay of drug concentrations.

The data obtained for admixtures prepared and stored at temperatures of 25°C and 4°C show the drugs have maintained at least 98% of the initial concentration. All solutions remained clear and colorless over the 14-day period, and the pH value did not change significantly.

The results indicate that admixtures of butorphanol tartrate 0.08 mg/mL and tropisetron hydrochloride 0.05 mg/mL in 0.9% sodium chloride injection solution were stable for 14 days when stored in polyolefin bags or glass bottles at 4°C and 25°C and protected from light. The infusion is feasible for manufacturing in pharmacy aseptic units and can be stored for up to 14 days for routine use in PCA infusions.

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F-CC and B-HZ conceived and designed the experiments. F-CC, X-YS, and PL performed the experiments. X-YS and J-GY analyzed the data. PL, J-GY, and X-YS contributed reagents/materials/analysis tools. F-CC, PL, and B-HZ wrote the article.

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**Abbreviations:** HPLC = high-pressure liquid chromatography, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting, RSD = relative standard deviation, USP = *United States Pharmacopeia*.

## INTRODUCTION

Drug treatment plays a major role in postoperative pain management. The required medicines are commonly delivered as a patient-controlled analgesia (PCA) with a number of drugs mixed together in a small volume and delivered by a syringe driver. Potential problems of mixing 2 or more injections together in infusion solutions include physical, chemical, or both changes that cause precipitation/crystallization and therefore reduce efficacy.<sup>1,2</sup>

Butorphanol tartrate is a morphinan-type synthetic opioid analgesic and is a  $\mu_2$ -receptor antagonist, a  $\mu_1$  agonist/antagonist, and a  $\sigma$ - and  $\kappa$ -receptor agonist. Similar to other opioid analgesics, the common adverse effects such as nausea and/or vomiting, somnolence, and dizziness are considerations with butorphanol.<sup>3,4</sup> Continuous intravenous administration of butorphanol has been proposed since the 1980s.<sup>5</sup> The drug may increase the incidence of postoperative nausea and vomiting (PONV),<sup>6</sup> which leads to discontinued administration. Thus, adjuvant medications are widely used to prevent PONV. One adjuvant is tropisetron hydrochloride, which is a selective antagonist of serotonin type 3 receptors (5-HT<sub>3</sub>).<sup>7,8</sup> Previous reports have suggested that adding tropisetron hydrochloride to PCA butorphanol tartrate for postoperative pain produces favorable analgesic effects and decreases the incidence of PONV.<sup>9,10</sup> In addition, the solution of butorphanol/tropisetron has been used for postoperative patients in our institution. However, the admixture of butorphanol tartrate and tropisetron hydrochloride for PCA use is not available commercially. An advance preparation of an admixture could improve security, time management, and speed of drug delivery to the hospital floor prior to administration. There is currently no information regarding the chemical stability and compatibility of the butorphanol–tropisetron mixture. Thus, the objective of the current study was to determine the compatibility and stability of the 2 drugs prepared with 0.9% sodium chloride injection and stored in polyolefin bags and glass bottles for a period of 14 days at 4°C and 25°C.

## METHODS AND MATERIALS

### Sample Preparation

Commercially available ampoules of butorphanol tartrate injection (1 mg/1 mL, lot number 13090432, Hengrui Medicine Co Ltd, Jiangsu, China, containing citric acid, sodium citrate,

sodium chloride, and benzethonium chloride for injection) and tropisetron hydrochloride injection (5 mg/5 mL, lot number 130101, CommScope Pharmaceutical Co Ltd, Hunan, China, containing sodium acetate, acetic acid, sodium chloride, and water for injection) were added to empty 100-mL polyolefin bags (Kelun Pharmaceutical Co, Sichuang, China) or glass bottles (Shangdong Pharmaceutical Glass Co Ltd, Shangdong, China). Then, 0.9% sodium chloride injection solution (Kelun Pharmaceutical Co, lot number A130604) was added to each container to produce a total volume of 100 mL. A rotary shaker was used to agitate the solution after each addition of fluid. The solutions were prepared using aseptic technique in a laminar airflow hood. The final concentrations of butorphanol tartrate and tropisetron hydrochloride were 0.08 and 0.05 mg/mL, respectively. These concentrations corresponded to those used in daily practice. This study was approved by the Medical Ethics Committee of the Dongfeng Hospital, Hubei University of Medicine (MEC-2013-015).

### Stability Study of the Analgesic Solutions

Three polyolefin and 3 glass containers containing the butorphanol tartrate and tropisetron hydrochloride admixture were stored in the dark at 4°C and 25°C. A 2-mL sample from each container was removed initially and at 1, 2, 3, 5, 7, 10, and 14 days after mixing. At each time point, the solutions were examined for color, cloudiness, precipitation, and gas production. The pH values for the samples at each designated time interval were determined using a pH meter (Model pHs-3C, Leici Instrument Co, Shanghai, China). All samples were then frozen at -20°C until analysis. The samples were allowed to reach room temperature before injection into the high-pressure liquid chromatography (HPLC) system. Each sample was assayed in triplicate.

### HPLC Assay

The HPLC instrumentation consisted of an UltiMate 3000 quaternary gradient pump equipped with a 20- $\mu$ L thermostated autosampler, and a diode-array detector (Dionex, Sunnyvale, CA). The HPLC data were acquired using chromatography management software (Chromeleon, version 6.80, Dionex, Voisins-le-Bretonneux, France). HPLC separation was performed on a Zorbax Hypersil ODS analytical column (150  $\times$  4.6 mm, 5.0  $\mu$ m, Agilent Technologies, Shanghai Branch, China). The detection of butorphanol tartrate and tropisetron hydrochloride was performed at a wavelength of 280 nm. All samples were assayed at ambient temperature. The mobile phase consisted of 0.05 mol/L potassium dihydrogen phosphate  $\text{KH}_2\text{PO}_4$  (Nanjing Chemical Reagent Co Ltd, Nanjing, China) and acetonitrile (HPLC grade, Agilent Technologies) in a ratio of 75:25 (v/v). The flow rate was 1.0 mL/min.

The analytical reference standards for butorphanol tartrate and tropisetron hydrochloride were obtained from the National Institutes for Food and Drug Control. The stock standard solutions of butorphanol tartrate 0.8 mg/mL and tropisetron hydrochloride 0.5 mg/mL were prepared in deionized water and frozen at -20°C. Fresh working standard solutions were prepared by diluting the stock solution with deionized water to the required concentrations before use.

Calibration curves were constructed from a linear plot of peak area versus concentration of the reference standards for butorphanol tartrate (16.0–160.0  $\mu$ g/mL) and tropisetron hydrochloride (5.0–100.0  $\mu$ g/mL). Three quality control samples (QCs) of butorphanol tartrate (40.0, 80.0, and 120.0  $\mu$ g/mL) and tropisetron hydrochloride (25.0, 50.0, and

75.0  $\mu$ g/mL) were used to calculate the accuracy and intraday and interday precisions. The accuracy and intraday precision were estimated using the recovery value and relative standard deviation (RSD, %), which were calculated from 3 QCs of butorphanol tartrate and tropisetron hydrochloride with 5 determinations per concentration on the same day. The interday precision (5 days) was also estimated as the RSD calculated from 5 replicate mixtures of samples prepared in the same way.

### Stability Indication

The stability-indicating capability of the chromatographic method was assessed using partially decomposed solutions of drug. The butorphanol tartrate and tropisetron hydrochloride mixture was 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 conditions. The samples were then assayed to confirm separation of the parent molecule from its degradation products.

### Analysis of Data

The data are expressed as mean  $\pm$  standard deviation (SD). At time zero, the initial concentration of both drugs was designated as 100.0%, and all subsequent concentrations were expressed as a percentage of the initial concentration. The stability was defined as a concentration within 90% to 105% of the initial value.<sup>11,12</sup> Therefore, a decrease from the mean initial concentration of more than 10% was considered a significant loss of the drug.

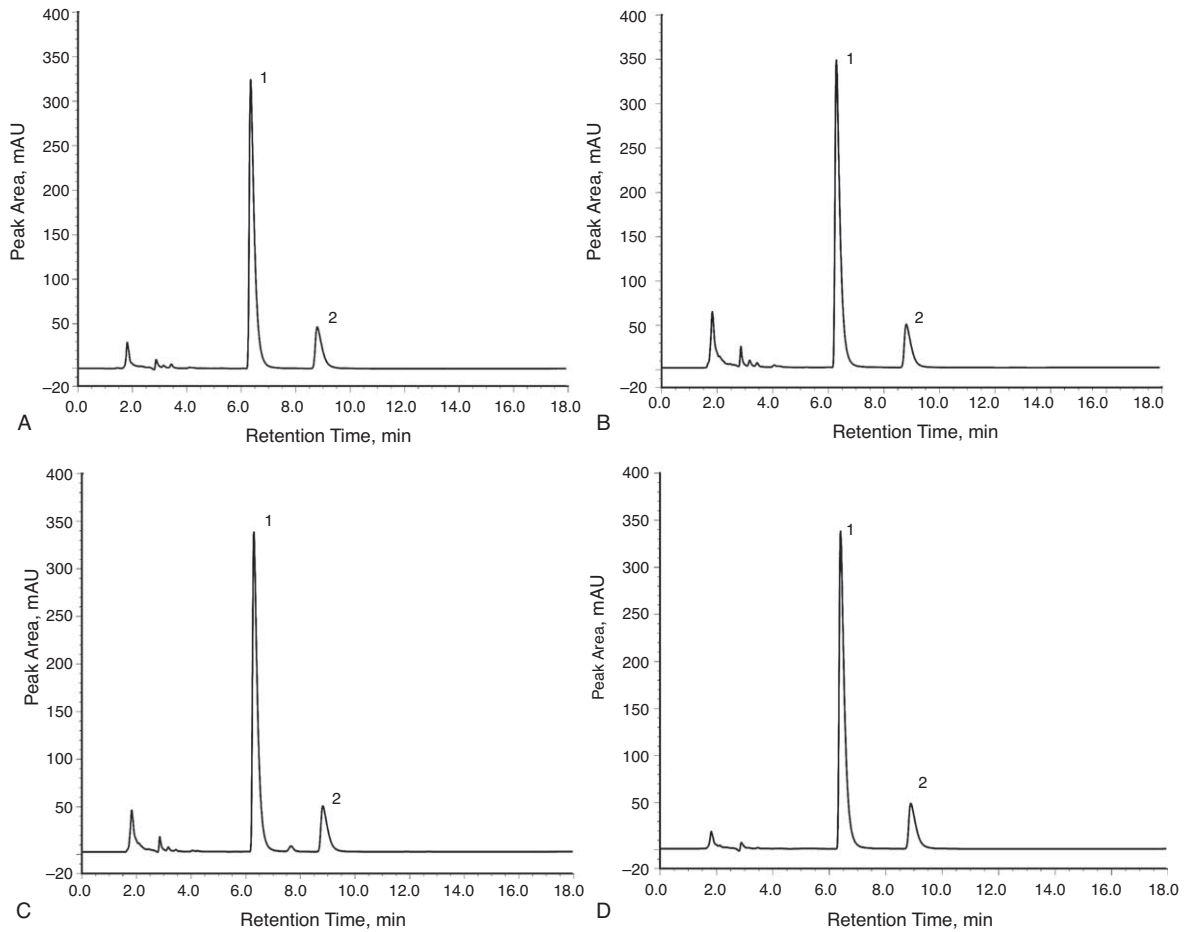
## RESULTS

### Validation of the HPLC Method

A new and simple HPLC method was developed and validated for the simultaneous determination of butorphanol tartrate and tropisetron hydrochloride in PCA solution. We found a linear response for butorphanol tartrate between the peak area and concentration with a correlation coefficient ( $r$ ) better than 0.9996 ( $y = 108.3x - 0.64$ ). For tropisetron hydrochloride, the linear regression analysis of the peak area of the drug concentration yielded a correlation coefficient ( $r$ ) better than 0.9991 ( $y = 1118x - 4.19$ ). The degradation study results showed that the decomposition products were less than 3% and separated from analytes and did not interfere with the quantification of butorphanol tartrate and tropisetron hydrochloride (Figure 1). The retention times were 8.9 minutes for butorphanol tartrate and 6.4 minutes for tropisetron hydrochloride. As shown in Table 1, the results obtained for the accuracy and the intraday and interday precision of the method were satisfactory for the recovery and RSD (%) values. As shown in this table, the intraday and interday RSD (%) were below 2.5% for both drugs and the recoveries obtained were close to 100%.

### Stability of the Analgesic Mixtures

The mixtures assayed can be considered as physically compatible because we did not observe evidence of incompatibility such as precipitation, turbidity, color change, opacity, and gas production. Tables 2 and 3 show the percentages of dose remaining for butorphanol tartrate and tropisetron hydrochloride in the admixtures when the tests were conducted at 25°C and 4°C, respectively. The concentrations of butorphanol tartrate and tropisetron hydrochloride remained greater than 98.0% in all admixtures. Additionally, there were no degradation



**FIGURE 1.** Chromatograms of butorphanol tartrate 0.08 mg/mL and tropisetron hydrochloride 0.05 mg/mL admixtures that were freshly prepared (A), exposed to 0.1 mol/L hydrochloric acid at 60°C for 5 hours (B), exposed to 0.1 mol/L sodium hydroxide at 60°C for 5 hours (C), and exposed to 3% hydrogen peroxide at 60°C for 5 hours (D). Retention times were 6.4 minutes for tropisetron hydrochloride (peak 1) and 8.9 minutes for butorphanol tartrate (peak 2). The other peaks were for degradation products. mAU = milliabsorbance unit.

products of butorphanol and tropisetron hydrochloride detected in any of the admixtures. During our 14-day experiment, the pH value was close to pH 3.3 and changes were within 0.1 U of the initial pH for all drug mixtures.

**DISCUSSION**

Combinations of different drug solutions are often used in clinical practice to relieve postoperative pain with the PCA

technique. However, little or no information is available regarding the chemical stability and compatibility of these analgesic mixtures. There are currently no commercially available analgesic mixtures, and the drugs must be prepared in the hospital pharmacy for clinical use. Thus, it is necessary to prove that drugs remain stable in admixture. Furthermore, it would be helpful if such combinations could be provided as ready-made mixtures to give greater assurance of sterility and

**TABLE 1.** Validation of HPLC Method

Compound	Measured Concentrations, mg/L	Accuracy, %	Precision RSD, %	
			Intraday	Interday
Butorphanol tartrate	40.0	101.2	0.5	1.2
	80.0	99.5	0.2	0.6
	120.0	99.8	1.0	2.0
Tropisetron hydrochloride	25.0	100.1	0.7	1.7
	50.0	99.6	0.4	0.8
	75.0	99.3	0.9	1.5

HPLC = high-pressure liquid chromatography, RSD = relative standard deviation.

**TABLE 2.** Percentage of Initial Concentration (mean  $\pm$  SD [%]; n = 3) of Butorphanol Tartrate (80 mg/L) and Tropisetron Hydrochloride (50 mg/L) Remaining After 14 d of Storage at 25°C in Polyolefin Bags or Glass Containers

Variable	Glass Containers		Polyolefin Bags	
	Butorphanol	Tropisetron	Butorphanol	Tropisetron
Initial concentration, mg/L*	81.03 $\pm$ 1.75	49.53 $\pm$ 0.81	81.19 $\pm$ 1.44	50.79 $\pm$ 0.21
Study day				
1	99.73 $\pm$ 1.52	99.83 $\pm$ 0.75	100.60 $\pm$ 0.16	99.88 $\pm$ 0.29
2	98.68 $\pm$ 0.94	99.14 $\pm$ 1.12	100.55 $\pm$ 0.70	99.99 $\pm$ 0.11
3	100.88 $\pm$ 0.42	100.63 $\pm$ 0.45	100.34 $\pm$ 1.01	99.81 $\pm$ 0.64
5	98.72 $\pm$ 0.41	101.07 $\pm$ 0.85	100.82 $\pm$ 0.33	100.35 $\pm$ 0.55
7	100.80 $\pm$ 0.95	100.68 $\pm$ 1.02	100.62 $\pm$ 0.98	99.91 $\pm$ 1.52
10	100.53 $\pm$ 0.63	100.66 $\pm$ 0.62	99.98 $\pm$ 0.11	99.39 $\pm$ 0.63
14	100.52 $\pm$ 0.18	100.78 $\pm$ 0.44	100.01 $\pm$ 0.66	99.60 $\pm$ 1.01

SD = standard deviation.  
\* n = 3.

availability<sup>13</sup> as well as to reduce the incidence of drug administration errors.<sup>14</sup>

Butorphanol tartrate, (–)-17-(cyclobutylmethyl)morphinan-3,14-diol[*S*-(*R*\*,*R*\*)]-2,3-dihydroxybutanedioate (1:1) (salt), is most closely structurally related to levorphanol. Due to its levorphanol structure, butorphanol tartrate has weak acidity with a  $pK_a$  9.86 and is stable in weak acid solution (pH 3.0–5.5). Tropisetron hydrochloride, (1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1*H*-indole-3-carboxylate hydrochloride (1:1), is a strong acid–weak base salt ( $pK_a$  8.9).<sup>15</sup> The solubility of tropisetron hydrochloride showed strong pH dependence, and the compound is stable in acid solution. Free tropisetron will precipitate in alkaline solution. The stability and compatibility tests of butorphanol tartrate alone or combined with other drugs in solution have demonstrated that butorphanol tartrate is a very stable drug.<sup>16–22</sup> None of the previous tests have found any loss of butorphanol tartrate during the testing. The previous studies also reported that most of the tested drugs such as droperidol, perphenazine, tramadol, fentanyl, and ropivacaine were stable and compatible in the presence of butorphanol tartrate. However, in the case of lornoxicam<sup>21</sup> or lansoprazole,<sup>22</sup> free lornoxicam or lansoprazole was found to precipitate when combined with butorphanol tartrate. This result was most likely

due to the acidic pH (3.0–5.5) of the butorphanol tartrate injection. There are 2 studies of tropisetron hydrochloride that assessed the stability and compatibility when diluted with either 0.9% sodium chloride or 5% dextrose and packaged in polyvinylchloride, polyolefin bags, and glass bottles. In both studies, tropisetron hydrochloride was stable for at least 14 days when stored at –20°C, 4°C, and 25°C.<sup>23,24</sup> However, in a study with fosaprepitant admixtures, tropisetron hydrochloride was found to be physically incompatible with fosaprepitant because of its alkaline pH value.<sup>25</sup>

In the present study, the pH of butorphanol tartrate–tropisetron hydrochloride mixtures was acidic and close to 3.3. However, there was no precipitation observed, and there was no modification of the chromatographic peaks when butorphanol tartrate was combined in solution with tropisetron hydrochloride. The stability and compatibility results showed that binary mixtures of butorphanol tartrate and tropisetron hydrochloride in 0.9% sodium chloride injection were stable for at least 14 days when stored in polyolefin bags and glass bottles at both 4°C and 25°C. It is important to note that drugs with pH-dependent incompatibility may present compatibility problems if combined or administered simultaneously with acidic drug solutions such as tropisetron hydrochloride or butorphanol tartrate.

**TABLE 3.** Percentage of Initial Concentration (Mean  $\pm$  SD [%]; n = 3) of Butorphanol Tartrate (80 mg/L) and Tropisetron Hydrochloride (50 mg/L) Remaining After 14 d of Storage at 4°C in Polyolefin Bags or Glass Containers

Variable	Glass Containers		Polyolefin Bags	
	Butorphanol	Tropisetron	Butorphanol	Tropisetron
Initial concentration, mg/L*	81.46 $\pm$ 1.21	51.33 $\pm$ 0.88	80.91 $\pm$ 0.95	51.09 $\pm$ 1.40
Study day				
1	100.29 $\pm$ 1.13	99.98 $\pm$ 0.20	100.18 $\pm$ 1.41	99.78 $\pm$ 1.70
2	99.75 $\pm$ 0.69	99.87 $\pm$ 0.51	100.71 $\pm$ 0.79	100.27 $\pm$ 0.45
3	98.48 $\pm$ 0.37	99.70 $\pm$ 0.56	100.52 $\pm$ 1.25	100.10 $\pm$ 1.25
5	99.24 $\pm$ 0.83	100.26 $\pm$ 0.39	100.65 $\pm$ 0.74	99.32 $\pm$ 0.63
7	100.47 $\pm$ 0.40	100.76 $\pm$ 0.51	100.90 $\pm$ 0.87	100.54 $\pm$ 0.17
10	102.51 $\pm$ 1.05	102.42 $\pm$ 1.49	101.27 $\pm$ 0.32	100.96 $\pm$ 0.28
14	100.41 $\pm$ 0.92	101.91 $\pm$ 1.22	99.68 $\pm$ 0.56	99.72 $\pm$ 0.84

SD = standard deviation.  
\* n = 3.

When mixing drugs taken from ampoules of sterile solutions, there is also the potential issue of bacterial contamination. We have examined the physicochemical stability without examining microbial contamination. In clinical practice it is necessary to follow Chapter 797 of the *United States Pharmacopeia* (USP)/National Formulary.<sup>26</sup> This regulation describes the compounding preparation of low-risk sterile products.<sup>27</sup> To ensure drug safety, the preparation should not be used for more than 48 hours after the date at room temperature or 14 days at refrigerated temperatures according to USP specifications.

## CONCLUSION

In summary, a reliable analytical HPLC method for the simultaneous determination of butorphanol tartrate and tropisetron hydrochloride in analgesic mixture samples was successfully developed. This 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 0.08 mg/mL and tropisetron hydrochloride 0.05 mg/mL in 0.9% sodium chloride injection were stable for at least 14 days when stored in polyolefin bags or glass bottles at 4°C and 25°C and protected from light.

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