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ORIGINAL RESEARCH

Stability of tramadol with three 5-HT$_3$ receptor antagonists in polyolefin bags for patient-controlled delivery systems

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Fu-chao Chen[1]
Jun Zhu[1]
Bin Li[1]
Fang-jun Yuan[1]
Lin-hai Wang[2]

[1]Department of Pharmacy, Dongfeng Hospital, [2]Department of Pharmacy, Renmin Hospital, Hubei University of Medicine, Shiyan, Hubei, People's Republic of China

Background: Mixing 5-hydroxytryptamine-3 (5-HT$_3$) receptor antagonists with patient-controlled analgesia (PCA) solutions of tramadol has been shown to decrease the incidence of nausea and vomiting associated with the use of tramadol PCA for postoperative pain. However, such mixtures are not commercially available, and the stability of the drug combinations has not been duly studied. The study aimed to evaluate the stability of tramadol with three 5-HT$_3$ receptor antagonists in 0.9% sodium chloride injection for PCA administration.

Materials and methods: Test samples were prepared by adding 1,000 mg tramadol hydrochloride, 8 mg ondansetron hydrochloride, and 6 mg granisetron hydrochloride or 5 mg tropisetron hydrochloride to 100 mL of 0.9% sodium chloride injection in polyolefin bags. The samples were prepared in triplicates, stored at either 25°C or 4°C for 14 days, and assessed using the following compatibility parameters: precipitation, cloudiness, discoloration, and pH. Chemical stability was also determined using a validated high-pressure liquid chromatography method.

Results: All of the mixtures were clear and colorless throughout the initial observation period. No change in the concentration of tramadol hydrochloride occurred with any of the 5-HT$_3$ receptor antagonists during the 14 days. Similarly, little or no loss of the 5-HT$_3$ receptor antagonists occurred over the 14-day period.

Conclusion: Our results suggest that mixtures of tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, or tropisetron hydrochloride in 0.9% sodium chloride injection were physically and chemically stable for 14 days when stored in polyolefin bags at both 4°C and 25°C.

Keywords: tramadol, ondansetron, granisetron, tropisetron, postoperative pain, patient-controlled analgesia

Introduction

Tramadol hydrochloride is a centrally acting synthetic analgesic with opioid and nonopioid actions and is commonly used for cancer and postoperative, gynecologic, and obstetric pain. Patient-controlled analgesia (PCA) with tramadol is a convenient regimen for postoperative pain and is popularly used in clinical practice; however, it is associated with troublesome side effects such as nausea and vomiting.[1,2] Postoperative nausea and vomiting (PONV), like postoperative pain, could reduce patients' postoperative satisfaction and comfort after surgery and result in delayed recovery, prolonged hospital stays, and economic losses. In order to reduce the incidence of PONV, various antiemetic agents, such as droperidol, metoclopramide, promethazine, ketamine, and 5-hydroxytryptamine-3 (5-HT$_3$) receptor antagonists, are usually administered with tramadol PCA.[3–6] Selective 5-HT$_3$ antagonists have been extensively studied and

Correspondence: Lin-hai Wang
Department of Pharmacy, Renmin Hospital, Hubei University of Medicine, 39 Chaoyang Road, Shiyan, Hubei 442000, People's Republic of China
Email wanglhpharmacy@sina.com

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are recommended in clinical practice guidelines for PONV prevention because they have fewer side effects than other antiemetics. Among the 5-HT_3 antagonists, ondansetron, granisetron, and tropisetron are the most widely used.[7]

Currently, there are no commercially available mixtures of tramadol and 5-HT_3 antagonists; therefore, they are prepared by mixing the respective drugs in 0.9% sodium chloride injection in aseptic units of hospital pharmacies and stored ready for PCA use. Mixing two or more drugs together in infusion solutions can lead to physical and/or chemical changes, which may result in variations in therapeutic properties and unknown side effects.[8,9] To our knowledge, no published information is available on the stability of tramadol when used in combination with 5-HT_3 receptor antagonists in a single solution for PCA administration. Thus, the objective of the current study was to determine the compatibility and stability of tramadol hydrochloride with ondansetron hydrochloride, granisetron hydrochloride, or tropisetron hydrochloride in 0.9% sodium chloride injection stored in polyolefin bags over a period of 14 days at 4°C and 25°C.

Materials and methods

Materials and reagents

The ethics committees of Dongfeng Hospital and Renmin Hospital approved this study. Reference standards of tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride were obtained from the National Institutes for Food and Drug Control (Beijing, People's Republic of China). Tramadol hydrochloride injection (100 mg/2 mL, lot number 879B01) was obtained from Grunenthal Pharmaceutical Co., Ltd. (Shanghai, China). Ondansetron hydrochloride injection (8 mg/4mL, lot number 30300916H) was purchased from Qilu Pharmaceutical Co., Ltd. (Jinan, China). Granisetron hydrochloride injection (3 mg/3 mL, lot number 141001) was supplied by Ningbo Team Pharmaceutical Co., Ltd. (Ningbo, China). Tropisetron hydrochloride injection (5 mg/5 mL, lot number 150106) was obtained from Jiangsu Hengrui Medicine Co., Ltd. (Jiangsu, People's Republic of China). A total of 0.9 mg/mL of sodium chloride injection (lot number A150826) used to prepare the sample mixtures was obtained from Sichuan Kelun Pharmaceutical Co., Ltd. (Sichuang, People's Republic of China). High-pressure liquid chromatography (HPLC) grade acetonitrile was purchased from Thermo Fisher Scientific (Waltham, MA, USA). The following reagents were of analytical grade: sodium acetate (Jinsha Chemical Co., Ltd., Shantou, People's Republic of China), acetic acid (Shanghai Jinlu Chemical Co., Ltd., Shanghai, People's Republic of China), and triethylamine (Shanghai Lingfeng Chemical Co., Ltd., Shanghai, People's Republic of China). Ultrapure water from a Milli-Q system (EMD Millipore, Billerica, MA, USA) was used in the study.

Instrumentation

The HPLC system used was UltiMate 3000 from Dionex Corporation (Sunnyvale, CA, USA) consisting of a quaternary-liquid gradient system, WPS-3000RS auto-injector, TCC-100 column oven, and DAD-3000RS UV spectrophotometer. A Zorbax Hypersil ODS (150×4.6 mm, 5.0 μm analytical column) from Agilent Technologies (Santa Clara, CA, USA) was used as the stationary phase. Chromatograms were recorded and analyzed using Chromeleon software Version 6.8 (Dionex, Voisins-le-Bretonneux, France). pH measurements were recorded using a precision pH meter (Model pHS-3C; Leici Instrument Co., Shanghai, People's Republic of China).

Chromatographic conditions

The mobile phase consisted of a mixture of 0.05 mol/L sodium acetate buffer (0.1% triethylamine) and acetonitrile in a ratio of 75:25 (v/v). The pH was adjusted to 4.0 using diluted acetic acid, and the mobile phase was filtered through a 0.22 μm filter. The flow rate of the mobile phase was maintained at 1.0 mL/min. The selected detection wavelengths for tramadol, ondansetron, granisetron, and tropisetron were 271 nm, 306 nm, 302 nm, and 285 nm, respectively. The assay was performed at room temperature, and the injection volume was 20 μL.

Preparation of stock and working solutions

Standard stock solutions of tramadol hydrochloride 10.0 mg/mL, ondansetron hydrochloride 1.6 mg/mL, granisetron hydrochloride 0.6 mg/mL, and tropisetron hydrochloride 0.5 mg/mL were prepared separately by dissolving appropriate amounts of drug in deionized water. These solutions were stored in amber bottles at −20°C and warmed to room temperature before use. The working standard solutions were prepared daily in amber-colored vials by diluting the standard solutions with water to the required concentrations.

Validation of the HPLC method

The HPLC method was validated for linearity, accuracy, precision, and stability of the four analytes. Linearity was demonstrated by running three replicates of the standard

solutions at six different concentrations over the ranges of 0.1–2.0 mg/mL, 0.001–0.032 mg/mL, 0.001–0.024 mg/mL, and 0.002–0.020 mg/mL for tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride, respectively. Calibration curves were obtained by plotting peak areas against drug concentrations. The coefficient of determination (r^2) was determined in each case. Replicate analyses (n=5) of quality control samples at three concentration levels (0.5 mg/mL, 1.0 mg/mL, and 1.5 mg/mL for tramadol hydrochloride; 0.004 mg/mL, 0.008 mg/mL, and 0.012 mg/mL for ondansetron hydrochloride; 0.003 mg/mL, 0.006 mg/mL, and 0.009 mg/mL for granisetron hydrochloride; 0.004 mg/mL, 0.005 mg/mL, and 0.008 mg/mL for tropisetron hydrochloride) were used for determining the precision and accuracy of the assay method. Precision was calculated as the coefficient of relative standard deviation (%) of the runs within a single day (intraday) and on different days (interday). The accuracy was calculated based on drug recovery from the solvents.

Stability indicating studies

The analytical methods for each of the drugs were validated as stable, which was indicated by accelerated degradation. The sample solutions of tramadol hydrochloride with three 5-HT_3 receptor antagonists in 0.9% sodium chloride injection were degraded with 0.1 mol/L sodium hydroxide (acidified), 0.1 mol/L sodium hydroxide (alkaline degraded), and 3% hydrogen peroxide (oxidized) for 5 hours at 60°C. The chromatograms for the degraded preparations were compared with the standard curves in order to detect any degradation products.

Preparation of mixtures of tramadol hydrochloride and 5-HT_3 antagonists

The mixtures of tramadol hydrochloride and the three 5-HT_3 antagonists were freshly prepared in infusion pumps using volumes reflecting those of 2-day pumps (100 mL). The final dose and concentration of each drug in the study were chosen by taking into consideration those more frequently used for postoperative pain via intravenous PCA.[3–5,10] The required amounts of the appropriate drugs were transferred to a polyolefin bag and made up to volumes of 100 mL with 0.9% sodium chloride injection. Binary mixtures containing the following final concentrations of the respective drugs were prepared: 10 mg/mL tramadol hydrochloride and 0.08 mg/mL ondansetron hydrochloride, 10 mg/mL tramadol hydrochloride and 0.06 mg/mL granisetron hydrochloride, and 10 mg/mL tramadol hydrochloride and 0.05 mg/mL tropisetron hydrochloride. Six samples of each solution were prepared and stored under the following conditions: three under refrigeration (4°C) and three at room temperature (25°C).

Physical compatibility and stability studies of the drug solutions

In the compatibility and stability study, samples were taken from each mixture for analysis of appearance, pH, and drug concentration at predetermined times (0 day, 1 day, 3 days, 5 days, 7 days, 10 days, and 14 days) after sample preparation. At the specified times, changes in color, cloudiness, and precipitation were evaluated against light and dark backgrounds. The pH of each solution was determined using a PHS-3C pH meter. On the day of analysis, samples were allowed to reach room temperature and diluted 1:10 with water before injection into the HPLC system. Each sample was analyzed in triplicate (total n=3). In addition, the concentration of each drug, obtained on each day of the study (remaining drug), was expressed as a percentage of its initial concentration in the respective mixture.

Data analysis

Data are expressed as mean ± standard deviation. The starting concentrations of tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride were defined as 100%, and subsequent concentrations were reported as a percentage of the initial concentration. The admixtures were considered chemically stable if they retained 90% of the initial concentrations. The changes in drug concentration with time were analyzed for each solution by using one-way analysis of variance. Statistical significance was considered when P-value was <0.05.

Results

Validation of HPLC method

A reversed-phase HPLC method was developed and validated in the current work for the simultaneous assay of tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride in analgesic mixture samples used in PCA. Under the current chromatographic conditions, the peaks for the four analytes were satisfactorily separated from each other. A typical chromatogram of standard solution containing the four analytes is shown in Figure 1. The average retention times for tramadol hydrochloride, granisetron hydrochloride, ondansetron hydrochloride, and tropisetron hydrochloride were found to

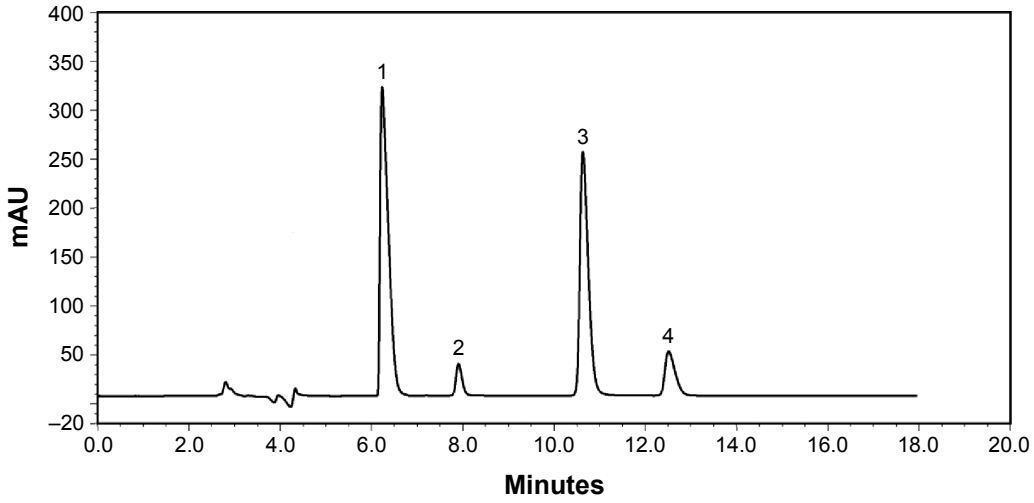

Figure 1 Chromatograms of standard drug mixture samples obtained after 20 μL direct injection.
Notes: Retention times were 6.3 minutes for tramadol hydrochloride (peak 1), 7.9 minutes for granisetron hydrochloride (peak 2), 10.7 minutes for ondansetron hydrochloride (peak 3), and 12.5 minutes for tropisetron hydrochloride (peak 4).

be 6.3 minutes, 7.9 minutes, 10.7 minutes, and 12.5 minutes, respectively. Under extreme conditions (strong acidic, basic, and oxidation solutions), these four analytes were found to be stable with <3% decomposition compounds and baseline separated from all analytes. The calibration curves for tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride were found to be linear over the concentration ranges of 0.1–2.0 mg/mL, 0.001–0.032 mg/mL, 0.001–0.024 mg/mL, and 0.002–0.020 mg/mL, respectively, with r^2 values being >0.999 in each case. Table 1 summarizes the results of the accuracy and the intraday and interday precision of the assay method for the four analytes. The data obtained showed that the proposed HPLC method is accurate and precise for the simultaneous assay of tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride in the sample mixtures.

Table 1 Validation of HPLC method

Compound	Measured concentrations (mg/mL)	Accuracy (%)	Precision, RSD (%)	
			Intraday	Interday
Tramadol hydrochloride	0.5	101.2	0.9	1.6
	1.0	99.4	0.4	0.8
	1.5	100.6	0.8	1.1
Ondansetron hydrochloride	0.004	98.8	0.5	1.9
	0.008	99.7	1.0	1.7
	0.012	101.1	0.4	0.8
Granisetron hydrochloride	0.003	98.7	0.8	1.4
	0.006	99.8	0.5	2.1
	0.009	100.2	0.6	0.9
Tropisetron hydrochloride	0.004	100.6	1.1	1.7
	0.005	101.5	0.3	1.2
	0.008	99.2	0.4	0.9

Abbreviations: HPLC, high-pressure liquid chromatography; RSD, relative standard deviation.

Physical and chemical stabilities of analgesic solutions

No precipitation or color changes were observed in the mixtures during the 14-day storage period. The results of the HPLC analyses for each of the test drugs are shown in Tables 2–4. No loss of tramadol hydrochloride was observed with any of the 5-HT_3 antagonists over the 14 days, after storage at either 4°C or 25°C. Similarly, little or no loss of ondansetron hydrochloride, granisetron hydrochloride, or tropisetron hydrochloride occurred over the 14 days. The average pH values obtained are given in Table 5. The change in the pH of infusions was considered insignificant over 14 days.

Discussion

Postoperative pain and nausea and vomiting are two of the major concerns of patients presenting for surgery. It is common practice in postoperative pain control to use combinations of drugs; the concept of combining multimodal analgesia with different drugs is aimed at providing superior pain relief and reducing the incidence of analgesic-related side effects compared with a single drug.[11] In addition, the use of a combination of different drugs in postoperative analgesia extends the time of analgesia, makes it more efficient, and allows the use of lower drug doses, which leads to less risk of side effects and drug dependence.[12] Based on the multimodal analgesia concept, several clinical studies have evaluated the efficacy of 5-HT_3 antagonists such as ondansetron,

Table 2 Stability of tramadol hydrochloride and ondansetron hydrochloride in 0.9% sodium chloride stored in polyolefin bags at 4°C and 25°C

Temperature	Drug	Initial concentration (mg/mL)[a]	Initial concentration remaining[a], mean ± SD (%)					
			Day 1	Day 3	Day 5	Day 7	Day 10	Day 14
4°C	Tramadol hydrochloride	10.3±0.46	99.7±0.4	100.8±0.3	100.9±0.4	99.4±0.2	101.8±0.1	101.4±0.2
	Ondansetron hydrochloride	0.083±0.005	100.1±1.5	102.2±1.0	102.1±2.6	100.3±1.3	101.4±1.1	102.3±1.5
25°C	Tramadol hydrochloride	10.3±0.49	99.8±0.4	98.6±0.1	100.2±0.2	99.7±0.3	101.5±0.2	99.8±0.2
	Ondansetron hydrochloride	0.082±0.004	100.9±1.9	100.3±0.4	101.1±1.6	101.6±0.2	97.9±0.3	101.6±0.7

Notes: [a]n=3. Data presented as mean ± standard deviation.
Abbreviation: SD, standard deviation.

Table 3 Stability of tramadol hydrochloride and granisetron hydrochloride in 0.9% sodium chloride stored in polyolefin bags at 4°C and 25°C

Temperature	Drug	Initial concentration (mg/mL)[a]	Initial concentration remaining[a], mean ± SD (%)					
			Day 1	Day 3	Day 5	Day 7	Day 10	Day 14
4°C	Tramadol hydrochloride	10.7±0.43	100.0±0.2	100.9±0.1	99.4±0.2	99.4±0.3	100.0±0.3	99.9±0.1
	Granisetron hydrochloride	0.062±0.004	100.7±0.5	101.6±0.6	101.5±1.0	100.3±0.9	101.7±2.1	100.5±1.0
25°C	Tramadol hydrochloride	10.3±0.38	99.6±0.1	101.6±0.5	100.7±0.1	101.9±0.2	101.2±0.1	101.5±0.1
	Granisetron hydrochloride	0.063±0.001	100.2±0.6	98.1±1.1	100.7±1.2	101.2±2.2	101.8±1.8	101.7±0.4

Notes: [a]n=3. Data presented as mean ± standard deviation.
Abbreviation: SD, standard deviation.

Table 4 Stability of tramadol hydrochloride and tropisetron hydrochloride in 0.9% sodium chloride stored in polyolefin bags at 4°C and 25°C

Temperature	Drug	Initial concentration (mg/mL)[a]	Initial concentration remaining[a], mean ± SD (%)					
			Day 1	Day 3	Day 5	Day 7	Day 10	Day 14
4°C	Tramadol hydrochloride	10.2±0.39	100.5±0.5	102.8±2.5	101.4±0.3	101.9±0.5	102.1±0.2	102.3±0.2
	Tropisetron hydrochloride	0.052±0.001	100.2±0.3	100.8±0.8	100.4±0.6	99.8±0.4	100.6±1.0	99.7±0.5
25°C	Tramadol hydrochloride	10.5±0.61	100.9±0.5	99.3±1.0	100.3±0.3	98.4±0.4	101.0±0.8	102.5±0.5
	Tropisetron hydrochloride	0.051±0.003	100.2±0.3	98.6±0.9	102.5±0.4	100.2±0.6	102.1±1.4	101.5±0.8

Notes: [a]n=3. Data presented as mean ± standard deviation.
Abbreviation: SD, standard deviation.

Table 5 pH values (mean ± SD [%]; n=3) of tramadol hydrochloride and 5-HT_3 antagonists in polyolefin bags at different storage conditions

Storage period (day)	Tramadol + ondansetron stored at		Tramadol + granisetron stored at		Tramadol + tropisetron stored at	
	4°C	25°C	4°C	25°C	4°C	25°C
0	6.25±1.5	6.19±0.2	6.66±0.9	6.68±1.0	5.52±0.2	5.46±0.2
1	6.21±0.6	6.21±0.4	6.62±0.6	6.57±0.7	5.54±0.2	5.49±0.1
3	6.27±0.2	6.24±0.0	6.68±0.2	6.55±0.1	5.55±0.3	5.46±0.1
5	6.25±0.1	6.21±0.8	6.75±0.2	6.72±0.3	5.59±0.0	5.52±0.8
7	6.25±1.3	6.25±0.2	6.68±0.8	6.63±1.2	5.54±0.4	5.41±0.6
10	6.27±0.1	6.26±0.1	6.72±0.1	6.66±0.5	5.62±0.1	5.55±0.3
14	6.22±0.1	6.23±2.1	6.70±0.9	6.70±0.6	5.58±0.2	5.51±0.1

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; SD, standard deviation.

granisetron, or tropisetron as adjuncts to tramadol PCA for treating postoperative pain. The studies suggested mixing the 5-HT_3 antagonists with the PCA solution for the prevention of tramadol-induced PONV.[3–5,10] However, such mixtures are not commercially available for clinical use, and they must be prepared in the hospital pharmacy departments under aseptic conditions. Information on the compatibility and stability of tramadol with ondansetron, granisetron, or tropisetron in infusion solutions for PCA is not available; therefore, the aim of this study was to address this issue.

Previously, stability and compatibility test on tramadol as a single drug, or in combination with other drugs in infusion solutions, have demonstrated that tramadol is a very stable drug. Under strong acidic and basic conditions, tramadol hydrochloride was found to be stable for 1 month when stored at temperatures ranging from 4°C to 50°C.[13] The studies also reported that most of the other tested drugs such as metoclopramide hydrochloride, droperidol, ketorolac tromethamine, alizapride, haloperidol, hyoscine *N*-butyl bromide, ketamine, dexamethasone, metamizole, ropivacaine, and bupivacaine were stable and compatible in the presence of tramadol hydrochloride.[14–26] In our study, the stability of tramadol hydrochloride was also demonstrated after exposing the samples under extreme pH and temperature conditions.

As for the 5-HT_3 antagonists, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride are strong acid–weak base salt (with pKa values as 7.4, 9.4, and 9.46, respectively). The aqueous solubility of the three 5-HT_3 antagonists showed strong pH dependence, which is stable in acid solution and may cause drug precipitation or crystallization in alkaline solution. Ondansetron hydrochloride has been found to be incompatible when combined in infusion solutions with acyclovir sodium, aminophylline, amphotericin B, fluorouracil, furosemide, ganciclovir sodium, lansoprazole, and sodium bicarbonate.[27–30] Previous studies on granisetron hydrochloride have also demonstrated incompatibilities with acyclovir sodium, amphotericin B, amsacrine, lansoprazole, and sodium bicarbonate.[31,32] Also, several studies[33,34] have revealed the instability of the drug mixtures containing tropisetron hydrochloride with lornoxicam or fosaprepitant, which seemed to precipitate because of pH modification.

In the present study, the pH of the three analgesic-5-HT_3 antagonist mixtures ranged between 5.4 and 6.7. No precipitation was observed in any of the mixtures. In addition, no changes were observed in the chromatograms after tramadol hydrochloride was combined with any of the three 5-HT_3 antagonists in the infusion solutions. The results obtained in our study indicate that mixtures containing tramadol hydrochloride combined with any of the three 5-HT_3 antagonists in 0.9% sodium chloride infusion solutions were stable for up to 14 days when stored in polyolefin bags at either 4°C or 25°C. The satisfactory stability of the drugs in the mixtures makes it possible to prepare them in advance by licensed central intravenous additive services, which may be convenient in hospitals.

Conclusion

A new and validated HPLC method for the simultaneous quantification of tramadol hydrochloride, ondansetron hydrochloride, granisetron hydrochloride, and tropisetron hydrochloride in analgesic mixture samples used in PCA has been successfully developed. The method was successfully used to study the stability of binary mixture of tramadol hydrochloride and three 5-HT_3 antagonists. The drugs were studied at concentration levels matching their usual doses in clinical practice. The results of the stability studies showed that mixtures of tramadol hydrochloride with ondansetron hydrochloride, granisetron hydrochloride, or tropisetron hydrochloride in 0.9% sodium chloride injection stored in polyolefin bags at 4°C or 25°C were chemically stable for 14 days.

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Disclosure

The authors report no conflicts of interest in this work.

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