

# Physical compatibility and chemical stability of dezocine and ramosetron in 0.9% sodium chloride injection for patient-controlled analgesia administration

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## Abstract

As an antiemetic, 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonist (ramosetron) is generally administered to prevent and treat postoperative nausea and vomiting induced by intravenous dezocine for patient-controlled analgesia. To date, the physicochemical stability of dezocine-ramosetron admixtures has not been assessed. The primary objective of this study was to evaluate the physicochemical stability of a combination of dezocine and ramosetron in 0.9% sodium chloride (normal saline [NS]) injections. Dezocine-ramosetron admixtures were prepared and stored in glass bottles and polyvinyl chloride (PVC) bags refrigerated at 4°C or stored at ambient temperatures (25°C) for up to 14 days. Initial concentrations were 5.0 mg/100 mL for dezocine and 0.3 mg/100 mL for ramosetron used as the diluents. Stability parameters (drug concentrations and pH values) were determined using high-performance liquid chromatography and pH measurements, respectively. Compatibility (cloudiness, discoloration, and precipitation) was assessed visually. After 14 days at 4 °C or 25 °C, the concentration losses of dezocine and ramosetron were both < 4%. Furthermore, there were no significant changes in color, turbidity, or pH values were observed in any of the batches. The results indicated that mixtures of dezocine and ramosetron in NS injections were continuously physically and chemically stable for 14 days in glass bottles or PVC bags stored at 4 °C or 25 °C.

**Abbreviations:** ADR = adverse reactions, HPLC = high-performance liquid chromatography, LOD = limit of detection, LOQ = limit of quantification, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting, PVC = polyvinyl chloride, RSD = relative standard deviation.

**Keywords:** compatibility, dezocine, patient-controlled analgesia, ramosetron, stability

## 1. Introduction

Currently, opioids are the most common drugs used to alleviate acute and moderate- to-severe chronic pain.<sup>[1]</sup> Opioids exhibit potent analgesia, although their action at  $\mu$ -opioid receptors causes adverse reactions (ADRs), such as addiction, respiratory depression, urinary retention, and constipation.<sup>[2]</sup> A method to reduce the undesirable side effects but retain potent analgesic properties involves discovering compounds that exhibit mixed agonist-antagonist or partial agonist activities for specific opioid receptors. This is because the activation of certain opioid receptors may have synergistic effects or produce fewer adverse effects than the activation of a single target.<sup>[3]</sup>

Dezocine (Fig. 1A), (5R, 11S, 13S)-13-amino-5, 6, 7, 8, 9, 10, 11,12-octahydro-5-methyl-5,11-methanobenzocyclodecen-3-ol, classified as a mixed agonist/antagonist analgesic that exhibits  $\mu$ -agonist and  $k$ -antagonist activities, was

introduced in the 1970s and approved as a prescribed analgesic by the FDA for the treatment of postoperative pain in 1986.<sup>[4]</sup> In comparison with opioid analgesics that act as full agonists, such as morphine, dezocine exhibits more effective or equivalent analgesia with mild ADRs and low addiction profiles.<sup>[5]</sup> Despite these advantages, dezocine remains associated with some ADRs, such as nausea and vomiting, that may lead to delayed recovery, longer hospitalization, and financial losses.<sup>[6]</sup>

Ramosetron hydrochloride (Fig. 1B), (1-methyl-1H-indol-3-yl)[(5R)-4,5,6,7-tetrahydro-1H-benzimidazol-5-yl]methanone hydrochloride, classified as a second-generation 5-HT<sub>3</sub> receptor antagonist, was approved as an antiemetic for the prevention and treatment of postoperative nausea and vomiting (PONV).<sup>[7]</sup> Ramosetron 0.3 mg was more effective in PONV prevention than ondansetron (4 mg), palonosetron (0.075 mg), and dexamethasone (10 mg).<sup>[8]</sup> Expert consensus and preclinical studies have indicated that ramosetron as an

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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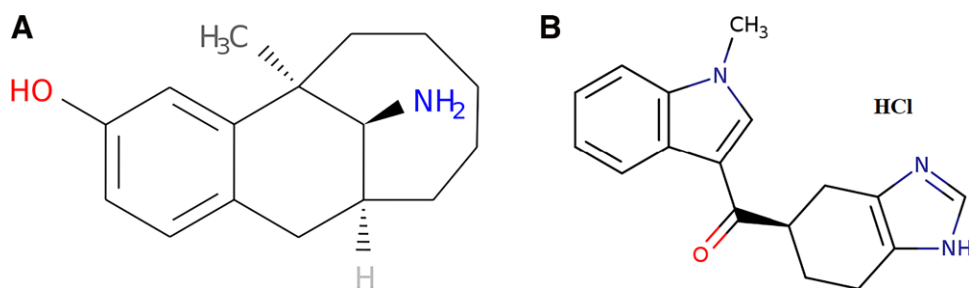
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**Figure 1.** Structures of (A) dezocine and (B) ramosetron hydrochloride.

adjuvant in combination with dezocine-based intravenous patient-controlled analgesia (PCA) for postoperative pain was not only the preferred analgesia but also lowered the incidence of PONV.<sup>[9,10]</sup>

Currently, emerging clinical interest in multidrug and multimode therapies has led to concerns regarding their roles in PCA administration. However, based on available data, binary admixtures of dezocine and ramosetron are not commercially available. Therefore, the admixtures can only be prepared by mixing the individual drug in 0.9% sodium chloride for injection by licensed central intravenous additive services, which may result in physicochemical changes.<sup>[11,12]</sup> Additionally, despite the therapeutic potential of the combination of dezocine and ramosetron as a common analgesic strategy for PCA administration, no concern has been placed on their compatibility and stability in saline. Therefore, this study assessed the physicochemical stability of a dezocine-ramosetron admixture prepared with NS in glass bottles and polyvinyl chloride (PVC) bags, which were stored at 4°C or 25°C for 14 days, and provide theoretical information on whether the mixtures are safe for clinical use.

## 2. Methods

### 2.1. Materials and reagents

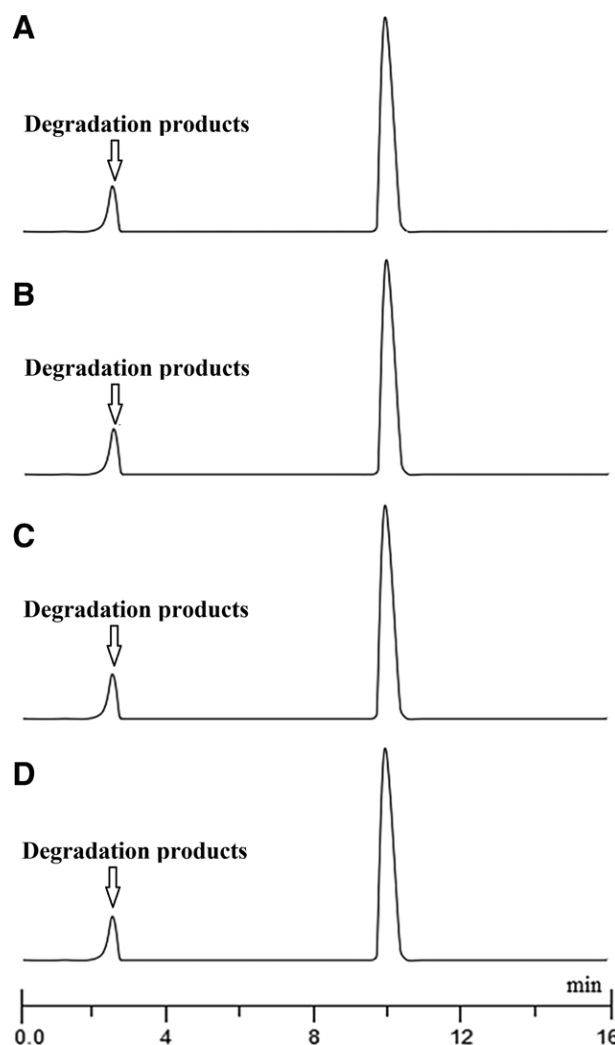
The 2 drug reagents tested were ampoules of dezocine (1 mL:5 mg) (Yangzijiang Pharmaceutical, Jiang Su, China) and ramosetron hydrochloride (2 mL:0.3 mg) (Astellas Pharmaceutical, Shenyang, China) injections. Standards of dezocine (lot number 171262-202002, purity 99.9%) and ramosetron hydrochloride (lot number 100662-201202, purity 99.5%) were obtained from the National Institutes for Food and Drug Control (Beijing, China). Sodium chloride (0.9%) was provided by Binhu Shuanghe (Wuhan, China). All other chemicals and reagents were of analytical grade (Guoyao Chemical Reagent, Beijing, China).

### 2.2. Instrumentation

Sample analysis and drug concentration measurements were performed using high-performance liquid chromatography (HPLC). Chromatographic analysis was performed using an LC-20AD HPLC system (Shimadzu, Japan): SPD-20A UV detector, CTO-10AS column oven, and LC-20AD pump with an LC solution/lite chemstation. The pH values of the samples were determined using an LP-PHS-25CW pH meter (Lepu Instrument Co., Changchun, China).

### 2.3. Chromatographic conditions

A Supersil ODS2 C<sub>18</sub> column (150 mm × 4.6 mm, 5 μm) (Elite, Dalian, China) was used for chromatographic separation. The mobile phase comprised 0.05 mol/L KH<sub>2</sub>PO<sub>4</sub> (pH 4.0, adjusted with phosphoric acid)-acetonitrile-tetrahydrofuran (75:20:5, v/v) and maintained at a flow rate of 0.5 mL/min. The injection



**Figure 2.** Chromatograms of dezocine 5.0 mg/100 mL that was 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). Dezocine elutes at 9.84 minutes.

volume was 10 μL per sample. The column temperature was set at 25°C, and the measurement wavelengths of the UV detector were 281 nm for dezocine and 245 nm for ramosetron, respectively.<sup>[13,14]</sup>

### 2.4. Preparation stock and standard curve solutions

The reference stock solutions of dezocine (5.0 mg/mL) and ramosetron hydrochloride (0.15 mg/mL) were prepared by

dissolving appropriate amounts in ultrapure water. The standard curve solutions (ranging from 0.75-25.0  $\mu\text{g}/\text{mL}$  for dezocine and 0.25-5.0  $\mu\text{g}/\text{mL}$  for ramosetron hydrochloride) were produced by diluting the stock solutions with appropriate amount of water. Calibration curves were prepared by running the standard solutions at 6 different concentrations.

### 2.5. Validation of the analytical method

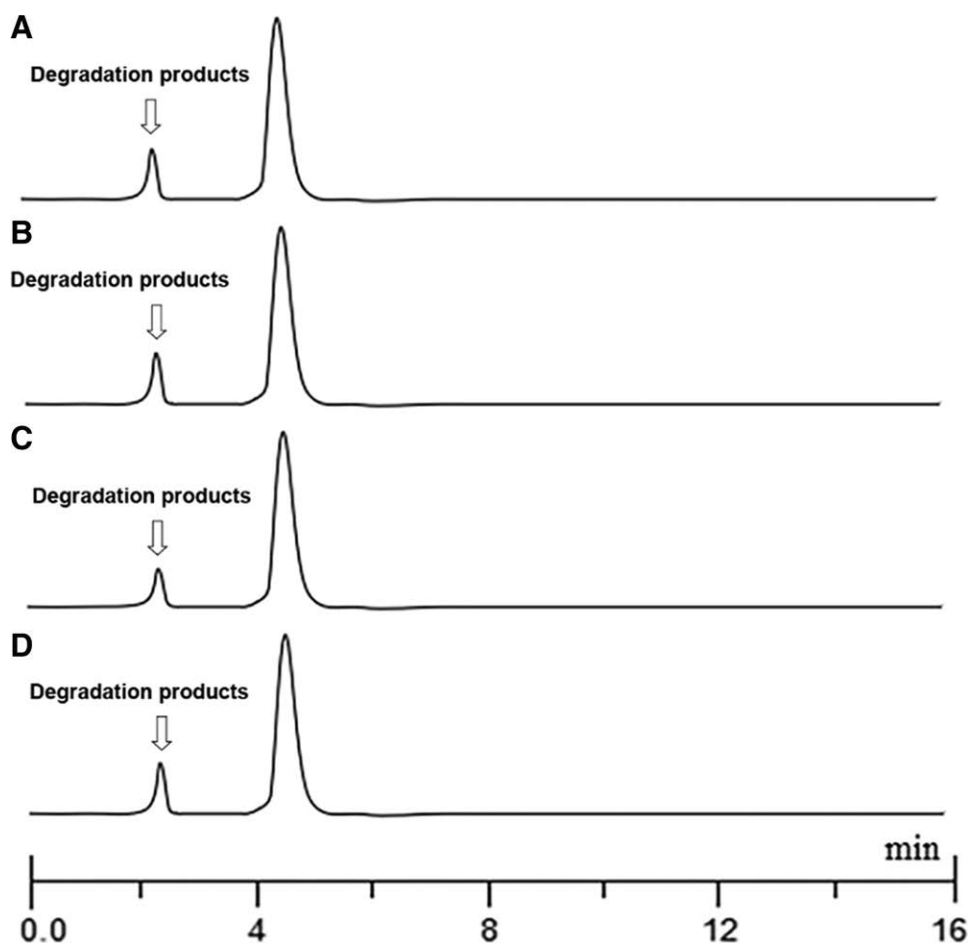
Different parameters, including the linearity, intra- and inter-day precision, accuracy, and stability of both drugs were assessed to validate the established HPLC assay. Linearity was examined by establishing a calibration curve comprising 6 different concentrations (triplicate) of dezocine and ramosetron standard solutions, ranging from 0.75 to 25.0 and from 0.25 to 5.0  $\mu\text{g}/\text{mL}$ , respectively. A calibration curve was plotted based on the ratio of the peak area to the corresponding standard drug concentration and validated using the correlation coefficient ( $r^2$ ). The accuracy and precision (intra- and inter-day) of the method were calculated according to the 3 quality control samples in quintuplicate for ramosetron (1.0, 2.0, and 4.0  $\mu\text{g}/\text{mL}$ ) and dezocine (4.0, 8.0, and 16.0  $\mu\text{g}/\text{mL}$ ). Precision was evaluated as the relative standard deviation (RSD, %), whereas accuracy was assessed by recovery. All replicates were analyzed on either 1 or 5 consecutive days. The limit of detection (LOD) and limit of quantification (LOQ) for the 2 drugs were determined using the signal-to-noise ratio method, 3:1 for LOD and 10:1 for LOQ.

### 2.6. Stability study of the admixtures

To obtain the final concentrations (selected based on routine clinical use) of dezocine (5.0 mg/100 mL) and ramosetron hydrochloride (0.3 mg/100 mL), dezocine (1 mL:5 mg) and ramosetron hydrochloride (2 mL:0.3 mg) injections were added into a 100 mL PVC bag or glass bottle. Subsequently, the container was diluted with the appropriate amount of NS with aseptic techniques in a laminar housing. At predetermined times (0, 1, 2, 3, 5, 7, 10, and 14 days), the admixtures were visually tested for appearance (color, clarity, and precipitation) against bright and dark backgrounds, and then the pH was measured. The concentrations of both drugs were measured and expressed as a percentage of the corresponding initial concentration. The prepared samples were stored at  $-4\text{ }^\circ\text{C}$ , then diluted in the ratio 1:2 with NS at room temperature for HPLC analysis. Finally, the samples in each container were measured in triplicates.

### 2.7. Study of stability indicators

In studying stability, the degraded samples in NS were detected by chromatographic concentration to determine the separation of degradation products from parent molecules. The testing solutions of dezocine, ramosetron hydrochloride and the admixtures of dezocine with ramosetron hydrochloride in NS were degraded under the conditions of 0.1 mol/L hydrochloric acid (acidified), 0.1 mol/L sodium hydroxide (alkalined), and 3% hydrogen peroxide (oxidized) for 5 hours at  $60\text{ }^\circ\text{C}$ .<sup>[15]</sup> The chromatogram and drug concentration of the degraded solution



**Figure 3.** Chromatograms of ramosetron hydrochloride 0.3 mg/100 mL that was freshly prepared (A), exposed to 0.1 mol/L hydrochloric acid at  $60\text{ }^\circ\text{C}$  for 5 hours (B), exposed to 0.1 mol/L sodium hydroxide at  $60\text{ }^\circ\text{C}$  for 5 hours (C), and exposed to 3% hydrogen peroxide at  $60\text{ }^\circ\text{C}$  for 5 hours (D). Ramosetron hydrochloride elutes at 4.66 minutes.

were evaluated through an HPLC assay that had been performed for all samples.

## 2.8. Data analysis

The test data for all samples are presented as the mean values and (mean  $\pm$  SDs). Linear regression analysis was used to calculate the concentrations of both drugs in each mixed solution at each interval. The percentage of the concentration of dezocine and ramosetron for subsequent samples relative to the corresponding initial concentration was calculated, and the drug was considered stable if the remaining amount was more than 90%. All statistical analyses were performed using SPSS 20.0 statistical software package (SPSS Corp. NY, Armonk), and statistical significance between groups was validated by a 2-ways analysis of variance followed by *t*-tests. Statistical significance was set at  $P < .05$ .

## 3. Results

### 3.1. Validation of the HPLC method for solution analysis

The concentrations of dezocine and ramosetron in the PCA admixture were simultaneously determined using a validated, rapid, and simple HPLC method. Based on the chromatographic conditions described above, both of the drugs were successfully separated. In addition, for dezocine, the linear relationship between the peak area and corresponding drug concentration was excellent, with a correlation coefficient ( $r$ )  $> 0.998$  (regression equation  $y = 1813.6 \times +197.31$ ). Ramosetron hydrochloride also had a linear relationship with a correlation coefficient ( $r$ )  $> 0.997$  (regression equation  $y = 1136 \times +55.31$ ). Even under extreme conditions (for instance, strong acidic, basic, and oxidation solutions), the degradation chromatographic results indicated that the decomposition products were not  $> 3\%$ , and separation from the analyte did not affect the quantitative and combined administration of each drug (Figs. 2–4). The average retention times for dezocine and ramosetron hydrochloride were 9.84 and 4.66 minutes, respectively. As summarized in Table 1, the RSD% of intra- and inter-day variations was not  $> 3.0\%$  for dezocine and ramosetron at 3 proportional concentrations, whereas the recovery rate was almost 100% for each drug. The LOD was 0.25  $\mu\text{g/mL}$  for dezocine and 0.08  $\mu\text{g/mL}$  for ramosetron hydrochloride, whereas the LOQ was 0.75  $\mu\text{g/mL}$  for dezocine and 0.25  $\mu\text{g/mL}$  for ramosetron hydrochloride.

### 3.2. Stability of the dezocine and ramosetron mixtures

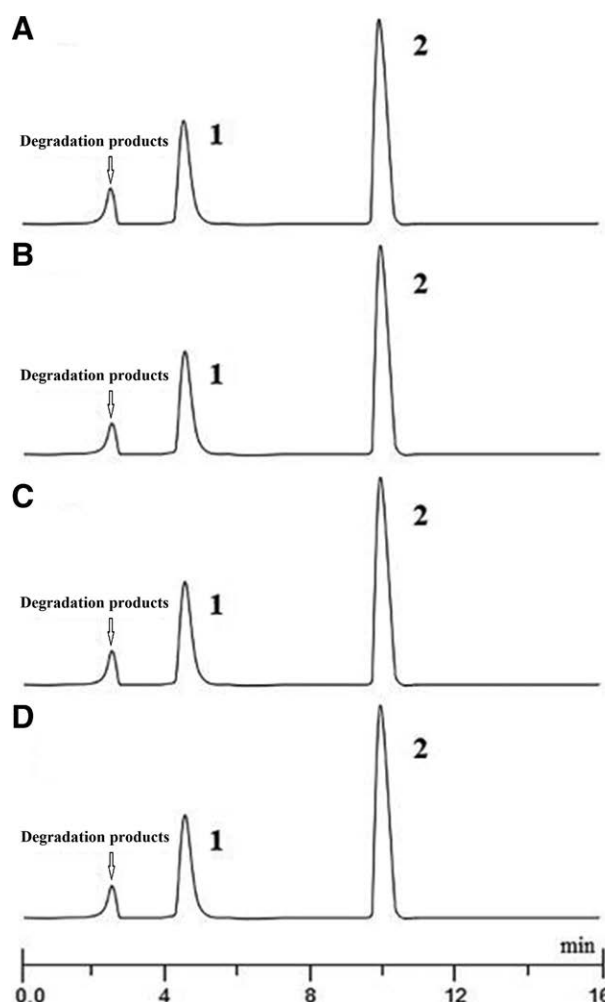
Relevant to this study, the compatibility data arising from the results indicated that no instability phenomena (such as color change, opacity, precipitation, or turbidity) were observed through visual insight in each admixture, proving that all the admixtures were physically compatible. Based on the stability data in Tables 2 and 3, the percentage of the concentration of dezocine and ramosetron for subsequent samples to the corresponding initial concentration in NS stored at 4 °C or 25 °C remained more than 96% in the binary admixtures. Additionally, as revealed by the typical chromatography analysis, during the accelerated degradation study, no degradation products were readily apparent in the binary admixtures from any of the chromatograms (Fig. 5). Furthermore, the variation of pH value in any of the batches was  $< 0.10$ , which was within the acceptable range.

## 4. Discussion

In comparison with single-modal analgesia, multi-modal analgesia can provide more effective abirritation owing to additive

or synergistic effects.<sup>[16]</sup> Nevertheless, few to no reports have been published regarding the physical or chemical changes in analgesic mixtures. Currently, few analgesics are available in the market, and these drugs are only prepared for clinical patients in hospital pharmacies. Therefore, the stability of all major drugs in analgesic mixtures urgently needs to be confirmed. In addition, good drugs stability and compatibility are very important for ensuring clinical efficacy and reducing ADRs caused by degradation products. Data arising from clinical reports have revealed that as an adjunct for dezocine PCA, ramosetron in combination with dezocine-based PCA for postoperative pain not only provides superior pain relief but also lowers the incidence of PONV.<sup>[10,17]</sup> However, no reports have been published regarding the physicochemical stability of the dezocine/ramosetron mixture. Therefore, this study aims to address this issue.

Preliminary studies have evaluated the physicochemical stability of dezocine injection alone or in combination with other drugs in infusion admixtures and have confirmed that dezocine is a highly stable drug. Fang et al discovered that dezocine was stable for 3 days at room temperature (25 °C) and for up to 14 days at refrigerated temperature (4 °C) in NS for PCA administration.<sup>[18]</sup> In addition, Hu *et al* indicated that the mixture of dezocine injection and ketorolac tromethamine in NS was stable for at least 12 hours at room



**Figure 4.** Chromatograms of dezocine 5.0mg/100mL and ramosetron hydrochloride 0.3mg/100mL 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). Dezocine elutes at 9.84 minutes (peak 2) and ramosetron hydrochloride elutes at 4.66 minutes (peak 1).

**Table 1****Validation of HPLC method for determination of dezocine and ramosetron.**

Compound	Measured concentrations, µg/mL	Accuracy % (n = 3)	Precision RSD % (n = 3)	
			Intraday	Interday
dezocine	4.0	98.3	1.8	2.2
	8.0	99.0	1.2	1.9
	16.0	98.7	1.5	2.5
ramosetron	1.0	99.2	0.9	1.5
	2.0	98.4	1.7	2.0
	4.0	98.8	1.9	2.6

HPLC = high-performance liquid chromatography, RSD = Relative standard deviation.

**Table 2****Percentage of initial concentration of dezocine (50 µg/mL) and ramosetron hydrochloride (3 µg/mL) remaining after 14 days of storage at 4°C in polyvinyl chloride bags or glass bottles (%; Mean ± SD; n = 3).**

Variable	Polyvinyl chloride bags		Glass bottles	
	Dezocine	Ramosetron	Dezocine	Ramosetron
Initial concentration, µg/mL	50.0 ± 0.03	3.0 ± 0.02	50.0 ± 0.02	3.0 ± 0.01
Day 1	100.6 ± 0.11	100.5 ± 0.10	100.7 ± 0.09	100.6 ± 0.07
Day 2	99.7 ± 0.14	99.9 ± 0.20	99.8 ± 0.11	100.0 ± 0.13
Day 3	99.2 ± 0.31	99.4 ± 0.35	99.3 ± 0.27	99.5 ± 0.33
Day 5	98.7 ± 0.29	99.0 ± 0.32	98.9 ± 0.28	99.1 ± 0.23
Day 7	98.2 ± 0.26	98.7 ± 0.42	98.3 ± 0.25	98.9 ± 0.22
Day 10	97.8 ± 0.29	98.6 ± 0.27	97.9 ± 0.32	98.8 ± 0.25
Day 14	97.3 ± 0.36	97.8 ± 0.32	97.5 ± 0.40	98.0 ± 0.35

RSD = relative standard deviation.

**Table 3****Percentage of initial concentration of dezocine (50 µg/mL) and ramosetron hydrochloride (3 µg/mL) remaining after 14 days of storage at 25°C in polyvinyl chloride bags or glass bottles (%; Mean ± SD; n = 3).**

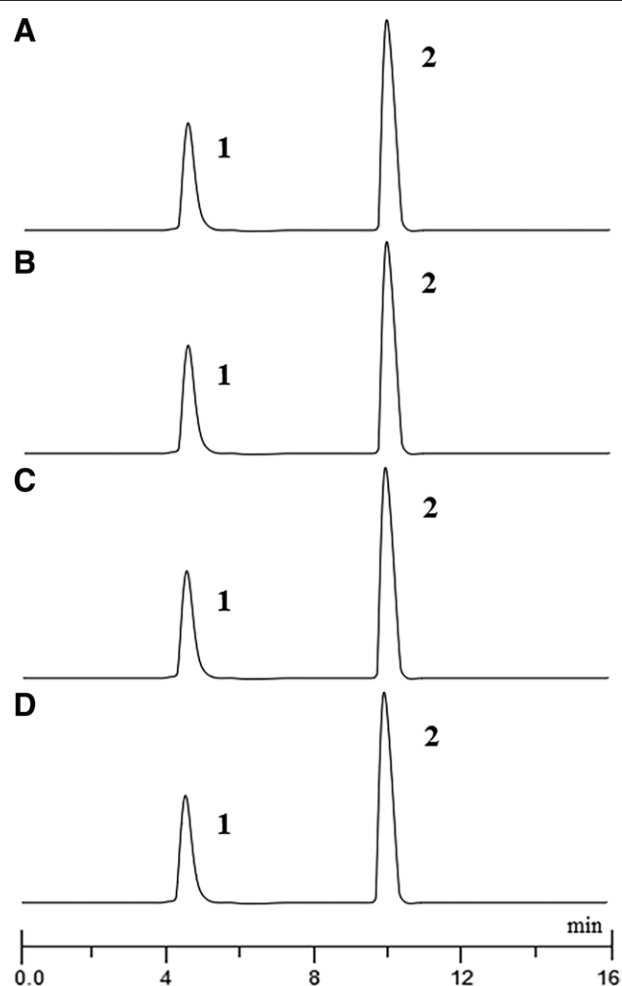
Variable	Polyvinyl chloride		Glass bottles	
	Dezocine	Ramosetron	Dezocine	Ramosetron
Initial concentration, µg/mL	50.0 ± 0.02	3.0 ± 0.01	50.0 ± 0.03	3.0 ± 0.01
Day 1	100.5 ± 0.13	100.2 ± 0.10	100.7 ± 0.07	100.3 ± 0.05
Day 2	99.7 ± 0.18	99.7 ± 0.25	99.7 ± 0.15	99.8 ± 0.20
Day 3	98.5 ± 0.21	99.2 ± 0.28	98.5 ± 0.19	99.1 ± 0.17
Day 5	97.5 ± 0.35	98.6 ± 0.40	97.5 ± 0.27	98.1 ± 0.35
Day 7	97.3 ± 0.26	97.8 ± 0.29	97.3 ± 0.26	97.9 ± 0.33
Day 10	97.2 ± 0.36	97.5 ± 0.30	97.2 ± 0.35	97.8 ± 0.25
Day 14	97.0 ± 0.27	97.3 ± 0.20	97.0 ± 0.36	97.6 ± 0.27

RSD = relative standard deviation.

temperature.<sup>[19]</sup> Chen et al confirmed that dezocine injection mixed with tropisetron hydrochloride in NS solutions was stable for up to 2 weeks, when stored at refrigerated or room temperatures.<sup>[20]</sup> The literature on the physicochemical stability of ramosetron hydrochloride alone or prepared with other agents in infusion admixtures is also limited. Song et al verified that ramosetron hydrochloride at a concentration of 0.3 mg/100 mL was stable when stored in NS or 5% glucose injection at room temperature for 10 hours.<sup>[21]</sup> Moreover, Xia et al reported that the mixture solution of 0.3 mg/100 mL ramosetron hydrochloride and 0.5 mg/100 mL midazolam hydrochloride was stable at room temperature or under refrigeration for 14 days.<sup>[22]</sup> He et al discovered that 100 and 200 µg/mL dexamethasone with 3.0 µg/mL ramosetron hydrochloride were physical compatible and chemical stable for up to 2 days in 5% glucose injection or NS injection in non-PVC infusion bags at 25°C.<sup>[23]</sup>

In this study, the analytical methods for dezocine and ramosetron hydrochloride were based on the preliminary studies.<sup>[20,22]</sup> The HPLC assay results revealed that the percentages of the concentration of dezocine and ramosetron for subsequent samples to the corresponding initial concentration were both > 96%. Throughout the study period, no color change or precipitation was observed in either PVC bags or glass bottles in any batch of samples. The measured pH values indicated that the pH of the binary solutions of dezocine and ramosetron ranged from 4.2 to 4.8, with a variation < 0.10. The satisfactory experimental data suggests that the mixed infusion of dezocine and ramosetron hydrochloride was physicochemically stable for up to 2 weeks when prepared in NS for PCA use.

Although the research results support the compatibility and stability of dezocine and ramosetron in NS, there may be an unexpected possibility of bacterial contamination when each drug is extracted from its ampoule for sterile



**Figure 5.** Typical chromatograms of dezocine and ramosetron hydrochloride admixtures on study 14 days. Mixtures stored at 25°C in glass containers (A) and polyvinyl chloride bags (B); Mixtures stored at 4°C in glass containers (C) and polyvinyl chloride bags (D). Dezocine elutes at 9.84 minutes (peak 2) and ramosetron hydrochloride elutes at 4.66 minutes (peak 1).

infusion.<sup>[24]</sup> In this study, we mainly considered the stability of the serial mixture, but ignored microbial contamination. In clinical practice, the standards for sterile preparations must be enforced, as recorded in Chapter 797 of the United States Pharmacopoeia.<sup>[25]</sup> However, the agents that we evaluated were categorized as low-risk compounding sterile products based on this regulation. To ensure the safety of the agents, the prepared solution should be stored at 25°C for 2 days as well as at 4°C for 2 weeks, according to the specifications of the United States Pharmacopoeia.<sup>[26]</sup> In addition, the PVC bags or bottles should be sterile, and all the infusions should be prepared in an aseptic environment in pharmacy intravenous admixtures.

## 5. Conclusion

In conclusion, the experimental results demonstrated that the PCA infusion containing 5.0 mg/100 mL dezocine and 0.3 mg/100 mL ramosetron hydrochloride in an NS injection were physically and chemically stable for up to 2 weeks when stored at 4°C or 25°C in glass bottles or PVC bags. To achieve excellent stability of the infusion mixed with dezocine and ramosetron, it is more suitable to prepare them in advance by licensed central additive services, which are very safe and reliable for clinical application.

## Author contributions

**Conceptualization:** Zhilei Guo.

**Data curation:** Zhilei Guo, Peng Chen.

**Validation:** Zhilei Guo.

**Writing – original draft:** Zhilei Guo, Peng Chen.

**Writing – review & editing:** Zhilei Guo.

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