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ORIGINAL RESEARCH

Compatibility and Physico-Chemical Stability of Six Intravenous Mixtures for Postoperative Multimodal Analgesia

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Purpose: To evaluate the physical-chemical compatibility of six drug combinations used in intravenous multimodal postoperative analgesia under differing storage conditions and different containers.

Methods: The analgesic mixtures studied were ternary and quaternary combinations of tramadol and ketamine with dexketoprofen or ketorolac, plus methadone in some mixtures, all diluted in saline solution. Physical compatibility, pH and concentration of drugs (ultra high performance liquid chromatography (UHPLC-DAD)) were determined 48 hours post-preparation (room temperature) and after 30 days (2°-8°C) for the mixtures in polyolefin bags, and after 14 days at room temperature for those mixtures in silicone and polyisoprene elastomers.

Results: No physical changes were observed, and pH remained stable throughout the study. For all five drugs in polyolefin bags the recovery percentage remained within the range 95–105%. Regarding mixtures prepared in elastomers, the recovery percentage for tramadol and dexketoprofen stayed within the range 95–105%, while for methadone it was less than 40%. A subsequent extraction with methanol demonstrated the methadone adsorption on the container walls, more pronounced in the silicone than in the polyisoprene reservoirs.

Conclusion: Analgesic mixtures of tramadol and ketamine with adjuvants (dexketoprofen or ketorolac, with or without methadone) showed physicochemical stability for 48 hours at room temperature and up to 30 days at 2°–8°C in polyolefin bags. However, the combination of tramadol, dexketoprofen, and methadone was unstable in both tested elastomeric devices due to methadone adsorption, making it unsuitable for clinical use. These findings underscore the critical role of container material in drug stability.

Keywords: compatibility, dexketoprofen, elastomer, ketamine, methadone, tramadol

Introduction

Introduced over two decades ago, multimodal analgesia is a practice strongly recommended by clinical guidelines for the treatment of postoperative pain.[1,2] Its rationale lies in seeking additive or synergistic effects by combining different drugs and analgesic techniques to achieve better pain control with less toxicity. This approach integrates regional anaesthesia and non-pharmacologic therapies into a comprehensive pain management plan, meticulously tailored to each patient, considering their condition, the type of surgery undergone, and the recovery phase.[3] Such a personalized approach not only enhances pain control but also stands as a fundamental component of Enhanced Recovery After Surgery (ERAS) protocols.[4]

For a variety of surgical interventions, the preferred method of analgesia administration is patient-controlled analgesia (PCA). PCA techniques allow patients to self-administer dose increments of analgesics, within safety intervals, according to their pain sensation, thus promoting pain control and patient satisfaction.[1,2,5] Furthermore, the use of elastomeric pumps is also a common practice when oral route is considered insufficient (especially after major outpatient surgery), due to their low cost and ease of use.[6,7] These devices are made up of a rigid plastic container that usually holds a silicone or polyisoprene reservoir where the drug solution is introduced. They allow the controlled infusion of medications intravenously or subcutaneously in the home setting.

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Regarding the drugs usually included in multimodal analgesia protocols, classic opioid analgesics via various routes of administration, and minor opioids such as tramadol, continue to play a fundamental role in controlling moderate to severe pain during the immediate postoperative period. The use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and N-methyl-D-aspartate (NMDA) antagonists such as ketamine are also recommended for their antihyperalgesic and opioid sparing effect.[8,9] In some cases, antiemetic drugs are added to analgesic mixtures in order to prevent postoperative nausea and vomiting (PONV).[10] In addition, dexmedetomidine and lidocaine are often included in opioid-free analgesia (OFA) mixtures.[11,12]

Given this wide range of pharmacological options, the combinations used in multimodal analgesia are highly diverse, as are the routes of administration and the types of containers employed. Although these drugs can be administered separately in the operating room, it is common practice to combine several drugs for intravenous infusion during the early postoperative hours. A study conducted in Spain highlighted the wide variety of analgesic mixtures used for different indications.[13] Nevertheless, it is important to note that mixing different substances could trigger physical and chemical transformations that might modify the therapeutic properties of the drugs, potentially diminishing their efficacy or inducing side effects, such as catheter occlusion or microembolisms.[14] Therefore, before combining several drugs in a diluent, it is essential to know if they are compatible from a physicochemical perspective. Despite the contributions of several authors to this topic,[15–17] the physicochemical stability and compatibility of these multidrug combinations remains underexplored. Specifically, the combination of tramadol with ketamine, often used together with NSAIDs such as dexketoprofen and ketorolac, and occasionally enhanced with methadone, is relatively common in our setting; however, concrete evidence on the physicochemical stability of these mixtures, particularly in elastomeric containers, is lacking.

In this context, the primary objective of this study was to evaluate the physical and chemical compatibility of six drug combinations used in intravenous multimodal postoperative analgesia under differing storage conditions and with different containers.

Materials and Methods

Analgesic Mixtures Under Study

The drug combinations chosen for the study are based on standard practice in our institution, but the same or very similar combinations are also commonly used in other institutions and settings.[13] It is worth to highlight that dexketoprofen (the active enantiomer of ketoprofen) was used in this study, as it is the intravenous formulation available in Spain and several other countries. The indications for use are identical, and no differences in chemical stability are expected between the two compounds. Table 1 shows the composition of the different mixtures studied.

The study received approval from the Ethics Committee of Hospital Clínic Barcelona.

Study Conditions

The diluent used in all cases was a saline solution (sodium chloride 0.9%). All mixtures were protected from ambient light with a light-protective bag, as most drugs used in the combinations are photosensitive.

Standard solutions were prepared in aseptic conditions according to accepted standardized procedures. Personnel compounding the mixtures were different from the team that analysed the samples. Three batches of each mixture were prepared from commercially available products (see Table 1). Samples were stored at room temperature (RT) or between 2°-8°C, depending on the study phase, and analyzed as in the following study points:

- a. V1, V2, V3, V4 stored for 48 hours at RT (simulating clinical practice administration): immediately after preparation (t_0), and at 24 and 48 hours post-preparation.
- b. V1, V2, V3, V4, stored for 30 days in refrigerated conditions (between 2°-8°C) (simulating the storage conditions in Pharmacy Department): immediately after preparation (t_0), and at 7, 15 and 30 days post-preparation.
- c. E1, E2, stored for 14 days at RT: immediately after preparation (t_0), and at 24 hours (clinical practice), 7 and 14 days post-preparation (Pharmacy storage).

All measurements were conducted in triplicate.

Table 1 Components and Study Conditions of Analgesic Mixtures (Diluent: Sodium Chloride 0.9%)

Mixture	Drug/Concentration (mg/mL)				Recipient	Study Condition
V1	Tramadol[e] 7.5 mg/mL	Dexketoprofen[f] 2.26 mg/mL	Ketamine[g] 0.19 mg/mL		Viaflo®bag[a] 100 mL	48 h RT[d] 30 days 2–8°C
V2	Tramadol[e] 7.5 mg/mL	Dexketoprofen[f] 2.26 mg/mL	Ketamine[g] 0.19 mg/mL	Methadone[h] 0.075 mg/mL	Viaflo® bag 100 mL	48 h RT 30 days 2–8°C
V3	Tramadol[e] 7.9 mg/mL	Ketorolac[i] 0.95 mg/mL	Ketamine[g] 0.95 mg/mL		Viaflo® bag 100 mL	48 h RT 30 days 2–8°C
V4	Tramadol[e] 7.9 mg/mL	Ketorolac[i] 0.95 mg/mL	Ketamine[g] 0.95 mg/mL	Methadone[h] 0.08 mg/mL	Viaflo® bag 100 mL	48 h RT 30 days 2–8°C
E1	Tramadol[e] 0.5 mg/mL	Dexketoprofen[f] 1 mg/mL	Methadone[h] 0.04 mg/mL		Autofuser® 100 mL[b]	14 days RT
E2	Tramadol[e] 0.4 mg/mL	Dexketoprofen[f] 0.8 mg/mL	Methadone[h] 0.04 mg/mL		Multirate Infusor Baxter LV®240 mL[c]	14 days RT

Notes: [a]polyolefin bag (inner layer of polyethylene); [b]silicone elastomer; [c]polyisoprene elastomer; [d]room temperature. Commercial products used: [e]tramadol hydrochloride 100 mg/2 mL (Normon Labs., Spain); [f]dexketoprofen trometamol 50mg /2 mL (Normon Labs., Spain); [g]ketamine hydrochloride 50 mg/mL (Ketolar™, Pfizer); [h]methadone hydrochloride 10 mg/ mL (Metasedin™, Esteve Pharmaceuticals); [i]ketorolac trometamol 30 mg/mL (Normon Labs., Spain).

Variables

Physical Compatibility

The mixture was considered physically incompatible in the presence of turbidity, colour change, and/or precipitation, compared to the standard solution at t_0. Turbidity was quantitatively assessed by nephelometry (HI 98713; Hanna Instruments, Eibar (Guipúzcoa), Spain), while colour change and precipitation were evaluated by direct observation on a white and black background, by two independent observers. Although qualitative, this method is widely used in stability studies.[18] In cases of doubt or discrepancy between observers, a third evaluator was consulted to reach consensus.

Chemical Stability

Following criteria established by ICH-Guidelines,[19] chemical instability was considered if a variation of ±5% in the concentration of any of the components of the initial mixture and pH values outside the stability range of any of the drugs (according to product technical specifications) were observed. Evaluation of pH was performed by potentiometry (Crison Basic 20®, Crison Instruments, S.A., Alella (Barcelona), Spain). The concentration of drugs in the mixtures was determined using Ultra High-Performance Liquid Chromatography with Diode Array Detection (UHPLC-DAD) (Acquity H UHPLC Class®), and expressed in the results as percentage of recovery, defined as the percentage of drug remaining in the mixture relative to the concentration measured at t_0.

Results

Chromatographic Method

Two UHPLC-DAD methods were developed in order to analyse the five drugs under study in a single chromatogram. Two reverse-phase columns (HSS: High-Strength Silica and BEH: Ethylene-Bridged Hybrid C18) were used, with acetonitrile/water as the eluent in gradient mode. The additive employed was a mixture of formic acid and ammonium formate (acidic pH) or ammonium formate and ammonia (basic pH). This allows the five drugs, with different pKa values, to elute in significantly different order depending on the pH of the mobile phase. The use of two orthogonal methods reduces the risk of interference from degradation products in the quantification of active principles.

Table 2 summarizes the main characteristics of the two developed methods. For all five drugs, the chromatographic method exhibited good injection repeatability (coefficient of variation: CV <1%) and good linearity between 0.5mg/L-500mg/L (r^2>0.999), with a detection limit at 215 nm between 0.1mg/L-0.3 mg/L. The accuracy of the method falls

Table 2 Chromatographic Conditions

Chromatographic Conditions: UHPLC-DAD Acquity UHPLC Class®		
	Method 1 (M1)	**Method 2 (M2)**
Column Mobile phase	Acquity HSS-C18® Acetonitrile/water + formic acid and ammonium formate (acidic pH)	Acquity BEH-C18® Acetonitrile/water + ammonium formate and ammonia (basic pH)
Flow rate	0.025 mL/min	
Injection volume	2 microlitres	
Forced degradation with HCl 1M, 80°C; NaOH 1M, 80°C; H_2O_2 15%, RT		
Linearity	0.5mg /L-500 mg/L (r^2>0.999)	
Detection limit	0.1 mg/L-0.3 mg/L (λ=215 nm)	
Accuracy	96–102%	
Precision	3.3%	

Abbreviation: RT: Room Temperature.

within 96%-102%, and precision ranges between 0.1%-3.3%. Both analytic methods are selective, successfully separating approximately 50 products generated in forced degradation studies.

Forced degradation under acidic conditions (1 M HCl, 80 °C), oxidative conditions (15% H2O2, 15–30 °C), and through photodegradation, confirms that there is no interference with degradation products.

Results in Polyolefin Bag Mixtures

In both the 48-hour room temperature study and the 30-day refrigeration study, no changes in colour, precipitation or turbidity were observed in the samples studied. The pH remained stable throughout the study, ranging between 7.08–7.28 for mixtures V1 and V2, and 6.76–6.91 for V3 and V4. For all five drugs in the four combinations, the recovery percentage remained within the range of 95–105% relative to the initial concentration (t_0), with a CV<5%. Furthermore, the results obtained with the two procedures did not differ by more than 2%, confirming the selectivity and accuracy of the results.

Figures 1 and 2 summarize the recovery percentages for the drugs present in mixtures V1, V2, V3 and V4.

Results in Elastomeric Pumps

No changes in colour, precipitation, or turbidity were observed in the samples studied at any of the analysed time points. The pH remained stable throughout the study, ranging between 7.0–7.3 for mixtures E1 and E2. The recovery percentage in the two analytical methods for tramadol and dexketoprofen stayed within the range of 95%-105% relative to the initial concentration (t_0) in both elastomers. However, the recovery percentage at 14 days for methadone was less than 40%, indicating a significant drug loss since t_0, and slightly faster in elastomer E1 (%recovery t_{24h}=57(E1) vs 67(E2)), as shown in Table 3.

In light of these results, the experiment was repeated for E1 and E2 mixtures in the same study conditions (14 days at room temperature) but using polyolefin bags as a recipient. In this case, the recovery percentage for all three drugs, including methadone, remained within the 95%-105% range.

Methadone Extraction with Methanol

Mixtures E1 and E2 were prepared again in Autofuser® 100 mL and Multirate Infusor Baxter® LV 240 mL elastomers. After 14 days at room temperature, the elastomers were emptied and filled with methanol. After 4 hours, a sample was taken to determine methadone concentration using the BEH column. The methadone concentration in E1 was 0.020 mg/mL (50% of the initial theoretical concentration), while in E2 the obtained methadone concentration was 0.006 mg/mL (15% of the initial

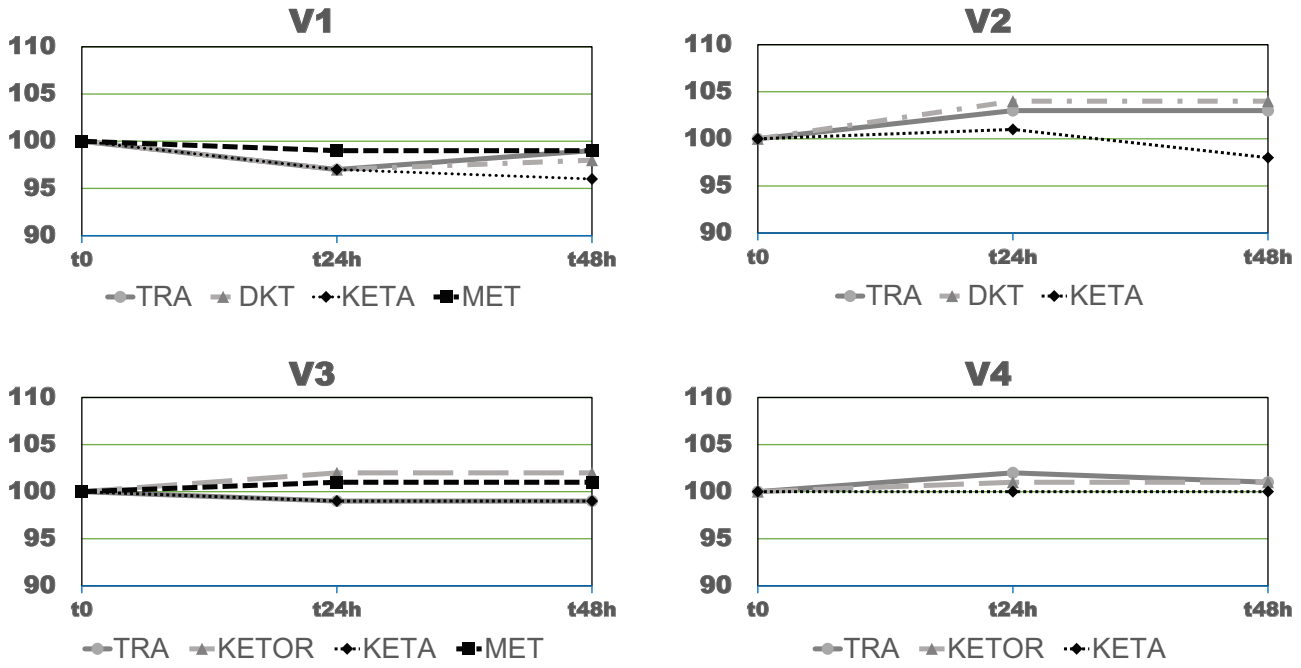

Figure 1 Recovery percentages of drugs in mixtures V1-V4 stored at room temperature for 48h.
Abbreviations: TRA, tramadol; DKT, dexketoprofen; KETA, ketamine; MET, methadone; KETOR, ketorolac.

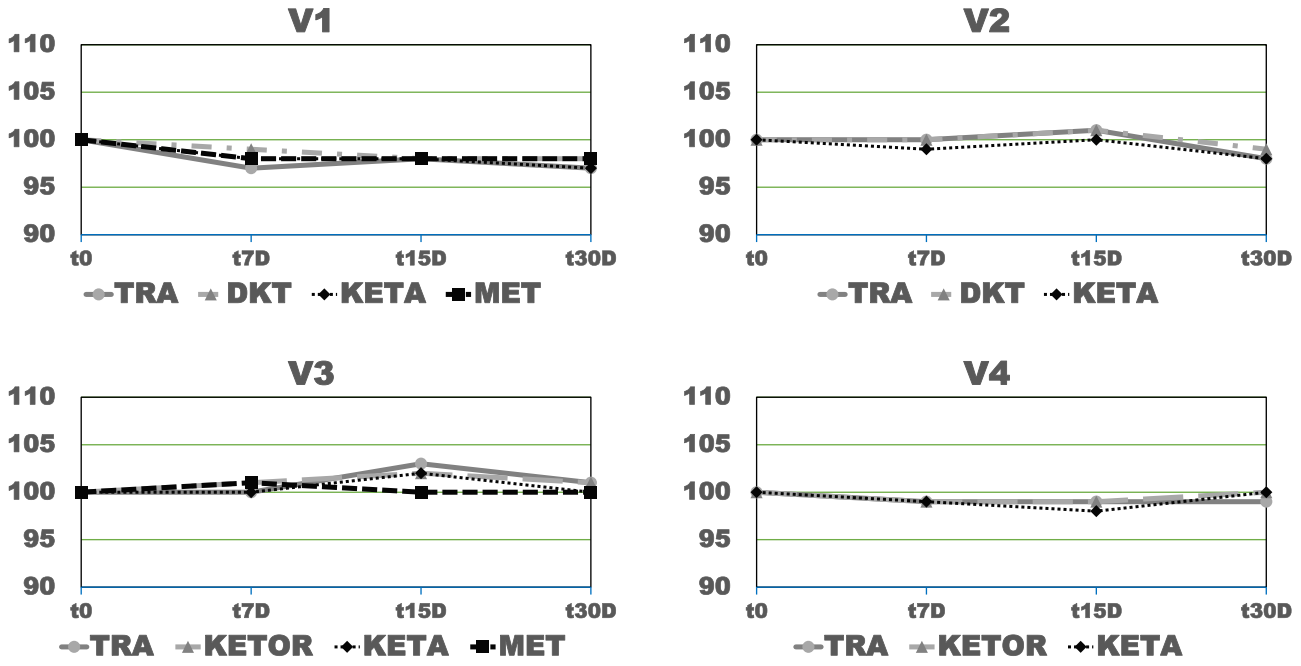

Figure 2 Recovery percentage of drugs in mixtures V1-V4 stored at 2°-8°C for 30 days.
Abbreviations: TRA, tramadol; DKT, dexketoprofen; KETA, ketamine; MET, methadone; KETOR, ketorolac.

theoretical concentration). Therefore, this experiment demonstrates that methadone is retained on the container walls in a considerable proportion, more pronounced in the silicone (Autofuser® 100 mL) than in the polyisoprene (Multirate Infusor Baxter® LV 240 mL) reservoirs.

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Table 3 Percentage of Drug Recovery in Elastomers

	Tramadol		Dexketoprofen		Methadone	
	E1	E2	E1	E2	E1	E2
t_o	100	100	100	100	70	75
t_{24h}	100	98	101	99	57	67
t_{7d}	98	98	101	97	31	43
t_{14d}	103	98	106	97	30	37

Notes: E1: Autofuser 100 mL (silicone elastomer); E2: Multirate Infusor Baxter 240 mL (polyisoprene elastomer).

Discussion

This study analysed the physicochemical stability of six intravenous mixtures for multimodal postoperative analgesia. The mixtures studied were combinations of analgesic and adjuvant drugs that are commonly used in intravenous postoperative analgesia. The synergistic combination of the opioid tramadol and the NSAID dexketoprofen (or ketoprofen) is widely supported by clinical practice, as is the use of small doses of ketamine for its opioid-sparing and antihyperalgesic effect.[1,2] Although ketorolac may not be as widely used due to its higher potential for adverse gastrointestinal effects, it remains frequently employed as an analgesic in trauma surgery in our setting.[20] The addition of methadone to these mixtures may be a controversial practice; however, it is defended by some authors due to the unique characteristics of this drug. Its high analgesic ceiling, efficacy in neuropathic pain, and antihyperalgesic effect, combined with its low addictive potential, make it an attractive option in postoperative analgesia to achieve optimal pain control with minimal doses.[6,21]

The importance of understanding the physicochemical stability of intravenous mixtures for patient safety has long been emphasized. Several authors have studied the stability of the combination of tramadol and dexketoprofen,[22] as well as the stability of tramadol with ketorolac[23] and tramadol with ketamine;[24] however, the stability of ternary and quaternary mixtures, such as those presented in this study, had not been known until now. Although the chemical stability of methadone combined with ketamine and lidocaine has been studied in the veterinary field,[25] there are very few studies on its physicochemical compatibility with other drugs, and most are based solely on evaluating physical compatibility.[26,27]

While intravenous mixtures for postoperative analgesia have a maximum duration of 48 hours, in this investigation the study was extended to 30 days (14 days for elastomers). The rationale is not only to verify stability during the administration period, but also to assess long-term stability under controlled conditions, thereby facilitating centralized preparation in the Pharmacy Service— a recommended practice for this type of complex mixture to maximize patient safety.[28]

One of the main findings of the study was confirmation of the effect that different types of containers might have on the same drug. Specifically, the amount of methadone in the mixture remains virtually unchanged when prepared in a bag, whereas, at a very similar concentration, it significantly decreases due to an adsorption phenomenon when the container is an elastomer. Moreover, this effect is more pronounced in silicone than in polyisoprene elastomers. This phenomenon of drug loss due to adsorption to the container walls has previously been documented in studies with other drugs. Mizogami et al reported a decrease in the initial concentration of bupivacaine, ropivacaine and mepivacaine, by 6%-14%, attributing this to hydrophobic interactions with the walls of the elastomer.[29] The degradation of methadone could lead to underdosing and poor analgesic outcomes, especially in patients with opioid continuous infusions. Based on these results, institutions may consider avoiding methadone in elastomeric pumps or switching to polyolefin bags for such mixtures.

All samples were analyzed using normal saline as a diluent. Although it is the most commonly used diluent, it would indeed have been interesting to also assess the stability of the mixtures in 5% dextrose; therefore, we consider this a limitation of the study. Similarly, it should be noted that the study results cannot be extrapolated to other concentrations or storage conditions different from those studied. Other elastomeric devices may exhibit similar behaviour to those analyzed in this study; however, given their widespread use and the specific implications they may have on drug stability, further studies in this area would be highly valuable.

The available therapeutic arsenal, including both classical analgesics and adjuvant drugs, as well as the recent rise of opioid-free analgesia, has led to a vast array of intravenous mixtures used in multimodal analgesia.[13] However, the safety of the use of such mixtures can only be guaranteed for those with available physicochemical stability data. For this reason, research in this field is necessary. Our study contributes new data to the existing body of evidence and may help guide formulation practices for PCA and ambulatory pain management, particularly with regard to potential drug–device interactions.

Conclusion

In conclusion, the four analgesic mixtures containing tramadol and ketamine combined with adjuvant drugs (dexketoprofen or ketorolac, with or without methadone), at the specified concentrations and diluted in saline solution within polyolefin bags (V1–V4), demonstrated both physical and chemical stability when stored for 48 hours at room temperature and up to 30 days under refrigerated conditions (2–8 °C).

In contrast, the mixture of tramadol, dexketoprofen, and methadone in the two elastomeric infusion devices evaluated (E1–E2) proved unstable due to methadone adsorption on the elastomeric internal surfaces. Therefore, its use under these conditions cannot be recommended in clinical practice.

These findings underscore the critical impact of container type on the stability of active pharmaceutical ingredients and support the need for drug–device compatibility assessments in the formulation of analgesic combinations.

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Disclosure

The authors report no conflicts of interest in this work.

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