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Beyond-use date of extemporaneous morphine hydrochloride oral solution

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ABSTRACT

Hospital pharmacists prepare morphine oral solution extemporaneously in Taiwan because of the unavailability of commercial products. According to the United States Pharmacopeia <795>, extemporaneous oral solution has an expiration of 14 days if there is no stability test data. However, outpatients usually need 4-week medications. The purpose of this study was to determine the beyond-use date of extemporaneous morphine hydrochloride (HCl) oral solution. Extemporaneous 0.1% morphine HCl oral solutions were prepared in an International Organization for Standardization (ISO) Class 8 compounding room, and bottled in 500-mL high-density polyethylene (HDPE) bottles with polypropylene caps. Twelve bottles were divided into 2 groups (sealed or opened daily) and stored under refrigeration or at room temperature to determine the chemical and microbial stabilities. Stability tests of the "sealed" group were performed after 4 weeks, while for the group in which the bottles were shaken and opened twice daily, stability tests were performed weekly. Chemical stability was determined by high performance liquid chromatography and pH, and microbial stability was determined by microbial limit tests according to pharmacopeias. In both groups, all the morphine HCl oral solutions retained more than 90% of the original concentration after 4 weeks, irrespective of whether they were stored at room temperature or in the refrigerator. The pH values were maintained at around 5 during the 4-week study period. All the refrigerated solutions passed the microbial limit tests within 4 weeks, regardless of whether they were sealed or opened twice daily. All the solutions stored at room temperature retained their microbial stability in the 1st week. However, mold and yeast counts exceeded the limits during the 2nd week in the "opened daily" group. Extemporaneous 0.1% morphine HCl oral solutions prepared in an ISO Class 8 clean room have a beyond-use date of 4 weeks in HDPE bottles when refrigerated. The beyond-use date decreased to 1 week when stored at room temperature. Extrapolation of this result may be limited by different compounding environments, containers or formulations.

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1. Introduction

Morphine is a narcotic analgesic widely used in pain control for trauma and cancer patients. However, the dosage varies according to severity of pain and adverse effects [1,2]. In Taiwan, only 5-mg and 10-mg immediate-release morphine tablets are available for acute pain control. Compared to immediate- and controlled-release morphine tablets, morphine oral solution has an earlier onset, is easier to take and more convenient for dose titration. Morphine solution is preferred in cancer patients who require tube feeding or have difficulties in swallowing. In our hospital, morphine solution accounts for 37%–40% of morphine prescriptions. Many hospital pharmacists have to prepare morphine oral solution extemporaneously because it is not available commercially. To ensure the quality of the drug, extemporaneously compounded drugs must be stored properly and have an appropriate beyond-use date (BUD) [3].

According to the United States Pharmacopeia (USP) <795>, an extemporaneous oral solution has a BUD of 14 days if there is no stability test data [3]. As some outpatients require 4-week medications, a BUD of 14 days cannot meet clinical needs. In addition, nursing stations usually do not have a refrigerator exclusively for Schedule I drugs like morphine. According to the literature, extemporaneous 0.1% morphine sulfate solution prepared from injection is stable for 91 days [4]. However, it is necessary to confirm if this applies to extemporaneous morphine hydrochloride (morphine HCl) oral solution prepared from raw material. The purpose of this study was to determine the storage conditions and BUD of morphine HCl oral solution through stability tests.

2. Methods

2.1. Sample preparation, reagents, chemicals and study design

The study samples (morphine oral solutions) were prepared from morphine HCl raw material obtained from the Taiwan Food and Drug Administration. It was dissolved in sterile water for irrigation to make a 1% morphine HCl solution, and further diluted with sterile water for irrigation to 0.1%. The final solution was placed in 500-mL high-density polyethylene (HDPE) bottles with polypropylene caps. All the preparations were performed in an International Organization for Standardization (ISO) 146441-1 Class 8 compounding room. The average temperature and humidity in the compounding room were 21.6 ± 1.4 °C and 64.6 ± 7.1%, respectively.

Twelve bottles of 0.1% morphine HCl solution were divided into 2 groups (sealed or opened daily) to determine the chemical and microbial stabilities. Six bottles were sealed after preparation. Three of them were stored at room temperature, and another three were refrigerated. Stability tests were performed after 4 weeks. Another 6 bottles were shaken and opened twice daily in a laboratory that was air-conditioned only in the daytime. Three of them were refrigerated, and another three were stored at room temperature in a laboratory where the humidity was 52%–65%, and temperature was less than 25 °C in the daytime and 25–28 °C in the evening and night. Stability tests were performed weekly on days 7, 14, 21 and 28.

Stability tests of pharmaceuticals usually include chemical, physical, microbial, therapeutic and toxicological stabilities [3,5]. As morphine solution may oxidize and discolor [6,7] and our product is preservative-free, this study focused on chemical and microbial stabilities.

High-performance liquid chromatography (HPLC)-grade solvents, such as methanol (mobile phase) and triethylamine (an alkylating agent of the mobile phase) were purchased from Merck KGaA (Darmstadt, Germany). Ammonium acetate and acetic acid (glacial), which are pH buffer agents of the mobile phase, were also purchased from Merck KGaA. Sodium 1-heptanesulfonate, a surfactant of the mobile phase, was from Fluka (Steinheim, Germany).

2.2. Equipment and analysis

All the analyses were repeated thrice. Chemical stability was determined through morphine assay by HPLC according to pharmacopeia and literature [3,8,9]. The linearity and repeatability of the morphine concentration analysis method used has been previously validated [10].

A sonicator (T710DH; Elma-Hans Schmidbauer GmbH & Co KG, Singen, Germany) was used for assay sample preparation.

A HPLC system (Agilent Technologies Inc., Palo Alto, CA, USA) consisting of a pump (G1311A), degasser (G1322A), photodiode array (PDA)-detector (G1315B) and autosampler (G1329A) was used to analyze the samples. The analytical column was a LiChroCART® 250-4 Purospher STAR RP-18e C_{18} column (250 × 4 mm, particle size 5 μm, from Merck, Inc., Darmstadt, Germany). Assay was performed according to the stability-indicating HPLC method for morphine [7]. Morphine was detected by UV absorption at 284 nm at a retention

Table 1 – Intra-day and inter-day repeatabilities of morphine HCl assay.

Morphine HCl concentration (mg/mL)	Day 1		Day 2		Day 3		RSD (%) of Day 1–Day 3
	Mean peak area	RSD (%)	Mean peak area	RSD (%)	Mean peak area	RSD (%)	
0.4389	2381.5	0.18	2383.1	0.14	2382.4	0.10	0.14
0.5486	2937.7	0.16	2944.1	0.13	2944.1	0.13	0.17
0.8229	4409.7	0.21	4412.6	0.09	4415.1	0.16	0.16

RSD = relative standard deviation; $n = 9$.

Table 2 – Recovery of morphine HCl in aqueous solution.

Theoretical concentration (mg/mL)	Assay results (mg/mL)	RSD (%)	Recovery (%)	Mean ± SD (%)
0.4389	0.4385	0.14	99.90	99.35 ± 0.44
0.5486	0.5427	0.17	98.92	
0.8229	0.8166	0.16	99.23	

RSD = relative standard deviation.

time of approximately 7.5 minutes. The mobile phase was a mixture of aqueous solution (containing 1% ammonium acetate, 1% acetic acid, 0.8% triethylamine and 0.017% sodium 1-heptanesulfonate) and methanol (85:15).

A pH meter (PHM210; Radiometer, Lyon, France) was used to determine the pH of the solution.

Microbial stability was determined by microbial limit tests according to USP <62>, <1111> and the Chinese Pharmacopeia (ChP) [3,9], which included *Escherichia coli*, molds, yeasts and total aerobes.

3. Results and discussion

3.1. *Physicochemical stability*

The chemical stability of morphine HCl oral solutions was assayed by HPLC according to the methods in pharmacopeias [3,9]. Linear response of the morphine HCl peak areas in the range of 0.215–0.860 mg/mL was demonstrated by a correlation coefficient greater than 0.999. The inter-day and intra-day repeatabilities of morphine HCl are shown in Table 1. All the inter-day and intra-day relative standard deviations (RSD) were less than 0.5%. Recovery was in the range of 99.35 ± 0.44% when 0.4389 mg/mL, 0.5486 mg/mL and 0.8229 mg/mL morphine HCl were analyzed (Table 2). In addition, the method was already proven [1,2] to be a stability-indicating HPLC method [10]. The results of the representative chromatograms of the standard of morphine HCl in water and samples of morphine HCl oral solutions are shown in Fig. 1. The retention time was 7.5 minutes in the standard and samples. All the morphine HCl oral solutions, whether sealed or opened twice daily, retained more than 95% (97.1–99.6%) of the original concentration after 28 days irrespective of storage temperature (Fig. 2, Table 3). The pH values were maintained at around 5 (5.34–5.66) during the 4-week study period under different storage conditions (Fig. 2). The color and clarity of the morphine solutions remained unchanged during the study period. Therefore, the solutions were chemically stable for at least 28 days whether sealed or open, refrigerated or stored at room temperature.

It has been reported that the major degradation products of morphine in aqueous solution are pseudomorphine and morphine-N-oxide due to its oxidative reaction [6,11,12]. More degradation is observed when morphine solution is in a higher pH of 2–7 or in an oxygen-rich environment [6,13–15]. On the contrary, light and temperature have less impact on stability, which is consistent with our findings. In our study, the morphine HCl oral solutions were stable at both room temperature and in the refrigerator when they were in an amiable weakly acidic condition (pH 5.3–5.7).

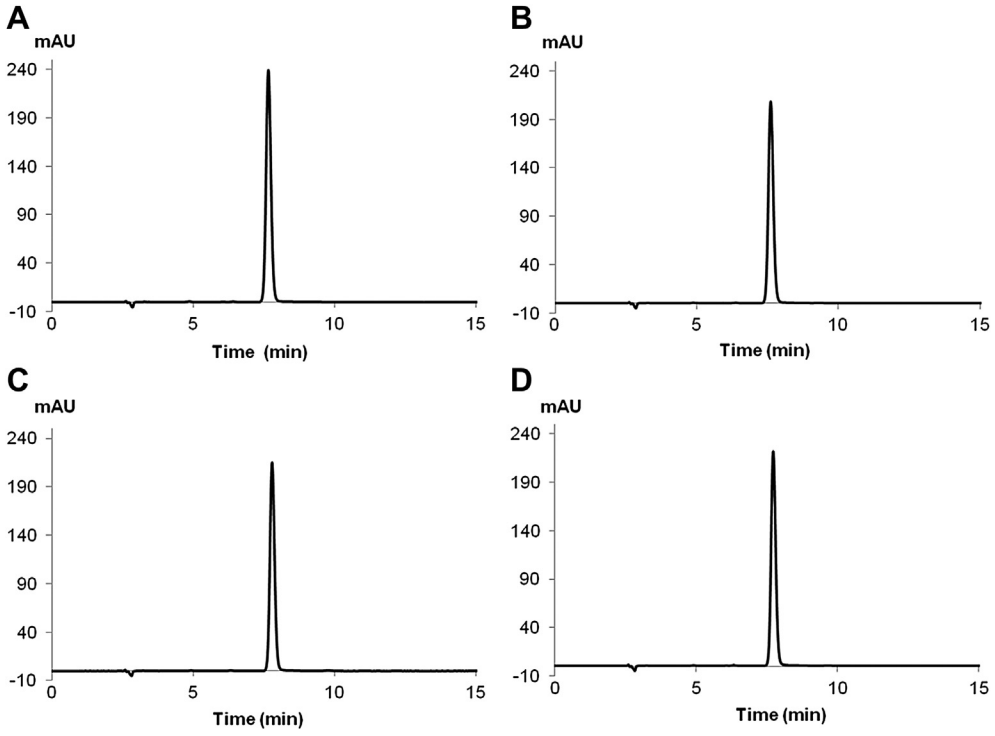

Fig. 1 – Representative chromatograms of 1.0 mg/mL morphine HCl in water: (A) standard; (B) sampled at Day 0; (C) stored for 28 days at room temperature; (D) stored for 28 days in the refrigerator. Morphine has a retention time of 7.5 minutes.

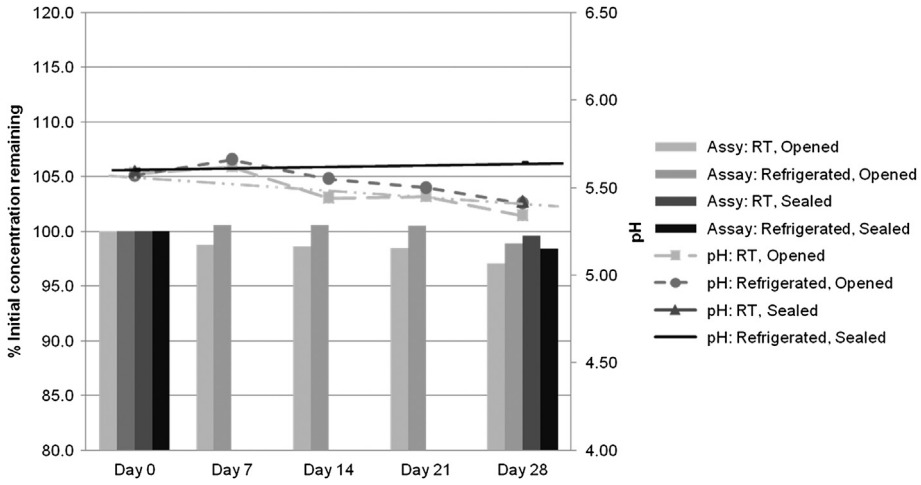

Fig. 2 – Chemical stability of extemporaneous morphine HCl solution. The bars and lines represent the morphine content compared to that on Day 0 and pH values, respectively, in different conditions of morphine HCl oral solution. The morphine content on Day 0 was considered to be 100%.

Discoloration from clear to light yellowish to brownish color has been observed when degradation products are found in morphine solution [6,12]. In our study, the samples of morphine HCl oral solutions remained clear during the 4-week experiment under all the storage conditions.

3.2. *Microbial stability*

According to microbial limit tests of USP <1111>, the total aerobic microbial count should not exceed 100 cfu/mL, total combined yeast/mold count should not exceed 10 cfu/mL, and no *E. coli* should be detected [3]. All the refrigerated solutions passed these microbial limit tests in the 4-week study period, regardless of whether they were sealed or opened twice daily (Table 4).

To prevent contamination from microorganisms, it has been suggested that preservatives be added to the extemporaneous aqueous solution [14,16–18]. If the addition of preservatives to the extemporaneous aqueous solution is contraindicated, the BUD can be set at 14 days when the solutions are stored under refrigeration [3]. Our study found that morphine HCl oral solution prepared with sterile water without the addition of any preservative can retain their microbial stability for 28 days when they are refrigerated. Microbial growth is unlikely in the solution under refrigeration whether the bottles are opened daily or not. However, when stored at room temperature, all the solutions in both groups retained their microbial stability in the 1st week only. The total combined yeast/mold count exceeded the limit (>10 cfu/mL) during the 2nd week in the "opened daily" group and during the 4th week in the sealed group. Daily opening influenced microbial stability when the solutions were stored at room temperature. According to our results, morphine oral solution shows both chemical and microbial stability at room temperature for at least 7 days. This provides evidence to allow morphine oral solution to be stored in a locked medication cart or space at room temperature and solves the problem of accommodating the bulky bottles in the limited refrigerator space that is generally found in nursing stations.

Table 3 – Chemical stability of extemporaneous morphine HCl solution.

Group	Opened	Opened	Sealed	Sealed
Storage temperature	Room temperature	Refrigerated	Room temperature	Refrigerated
	Mean concentration (mg/mL)			
Day				
0	0.953 ± 0.020	0.943 ± 0.010	0.938 ± 0.012	0.945 ± 0.008
7	0.941 ± 0.002	0.949 ± 0.011	NA	NA
14	0.939 ± 0.003	0.949 ± 0.006	NA	NA
21	0.938 ± 0.004	0.948 ± 0.012	NA	NA
28	0.925 ± 0.006	0.932 ± 0.008	0.934 ± 0.017	0.930 ± 0.006

NA = not available.

Table 4 – Microbial limit tests of extemporaneous 0.1% morphine HCl oral solution.[a]

Day	Room temperature			Refrigerated		
	Total aerobes	Yeasts and molds	*E. coli*	Total aerobes	Yeasts and molds	*E. coli*
Opened twice daily						
0	Pass	Pass	Pass	Pass	Pass	Pass
7	Pass	Pass	Pass	Pass	Pass	Pass
14	Pass	**Fail**	Pass	Pass	Pass	Pass
21	Pass	**Fail**	Pass	Pass	Pass	Pass
28	Pass	**Fail**	Pass	Pass	Pass	Pass
Sealed and stored						
0	Pass	Pass	Pass	Pass	Pass	Pass
28	Pass	**Fail**	Pass	Pass	Pass	Pass

cfu = colony forming unit.
a According to USP <1111>, aerobes should not exceed 100 cfu/mL, yeasts and molds should not exceed 10 cfu/mL, and no *E. coli* should be detected.

4. Conclusion

According to our chemical and microbial stability tests, extemporaneous 0.1% morphine HCl oral solutions prepared in an ISO Class 8 compounding room with an average temperature of 21.6 °C and humidity of 64.6%, and bottled in HDPE bottles with polypropylene caps, has a BUD of 4 weeks when refrigerated. When the bottle was opened twice daily in a room, mimicking patients' homes that tend to be air-conditioned for only 9–10 hours a day, the BUD decreased to 1 week when stored at room temperature because of microbial instability. We therefore recommend that patients store the solution in the refrigerator. However, at a nursing station in a hospital where there is 24-hour air-conditioning, the morphine solution may be locked in the medication cart for 1 week. Microbial stability is a major concern in determining storage condition and the BUD for an extemporaneous oral aqueous solution. Extrapolation of this result may be limited by different compounding environments, containers or formulations.

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