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Chemical compatibility of midazolam and morphine in 5% glucose solution

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Abstract. To date, data on compatibility of midazolam and morphine in 5% glucose under ambient temperature and light are lacking. This study assayed compatibility of midazolam and morphine after reconstitution under conditions commonly practiced in the hospital. Solution of midazolam and morphine was prepared by diluting 5% glucose to a 50 mL syringe injection to a final concentrations of 0,58 mg/mL for Midazolam and 96 µg/mL for morphine were achieved. The triplicate solutions were stored at ambient temperature under either mixed daylight. The aliquot sample was taken from syringe at times 0, 8, 24, 72, 120, and 168 hours. The aliquot part solutions were examined for visual inspection, pH and concentration changes assayed by high-performance liquid chromatography. The sample of midazolam and morphine were clear, no turbid, no gas, and no colour changes during 168 hours. The concentrations of midazolam, and morphine at 168 hours were retained ±90% compared to freshly prepared solution. This result concluded that solutions of midazolam and morphine in 5% glucose could be stored in syringes injection at ambient temperature up to 168 hours.

Keywords: *Compatibility, Morphine, Midazolam, 5% glucose*

1. Introduction

Midazolam and morphine were the drugs most extensively used in paediatric critical care [1]. Both of those analgesics are administered through continuous infusion for achieving stable concentration. To achieve the accurate concentration, these medications are diluted in proper solution; this modification may change the compatibility of the original formulation [2].

A hospital undertaking pharmaceutical compounding must ensure that the drug is stable and appropriate prior to administration. Stability contributes to ensuring a correct therapeutic response during treatment. When instability forms degradation by-products, this can have three consequences: unacceptable performance, therapeutic failure or a toxic effect[3]. Therefore, research specifically on stability is of value as it improves the evidence supporting hospital pharmacy practice.

To date, the published data are often not appropriate for conditions in hospitals. Data on stability of reconstituted midazolam and morphine is widely diluted in normal saline (NS) and (sterile) water for injection (WFI)[4-7']. One of them, testing on morphine stability in 5% glucose but under protection from light[8], meanwhile, these medications are often used under light condition.

The above mentioned performed the importance of this study to investigate the stability of midazolam and morphine during storage and administration time after dilution. This study confirms whether is safe to store midazolam and morphine diluted in 5% glucose up to 7 days. The result of stability study op to 7 days allows prefilled solution of midazolam and morphine in pharmacy unit.

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2. Methodology

2.1 Design study

This study aims to determine the physical and chemical compatibility of midazolam and morphine in 5% glucose under ambient temperature. The aliquot solution were examined at zero (0) hours, eight (8) hours, 24 hours, 48 hours, 96 hours and 168 hours for visual inspection, pH measurement and concentrations by high pressure liquid chromatography (HPLC).

2.2 Preparation of test solutions

Morphine (Kimia Farma, Indonesia), Midazolam (Novell Pharm Lab, Indonesia), and 5% glucose (Widatra, Indonesia) was obtained from hospital pharmacy. The medications were assessed at the concentrations typically used in children. Both of medications were prepared by 50 mL syringe in triplicate. The reconstituted solution was stored in 50 mL syringes under room temperature, light, and humidity. Room temperature and humidity were monitored during experimentation and were within the ranges of 25–28 ° C and 70–80% relative humidity (RH). Five milliliter (mL) aliquot solutions were taken for visual inspection and pH measurement. A 1 mL aliquot solution was drawn for HPLC assay at each sampling time.

2.3 Compatibility Assay

Physical compatibility was evaluated used unaided eye to check the turbidity, gas formation, and color changes by two people. Observation was undertaken using a black background to show haziness or white background to demonstrate color changes. The solution was justified as incompatible if any turbidity, effervescence, discoloration, haziness, or precipitation.

Chemical compatibility was based on pH and concentration. The pH of aliquot samples were measured with a calibrated pH meter, Mettler Toledo 1120/1120-X (Urdorf, Switerland). A change in pH of more than a half unit is considered as incompatibility.Concentration was performed with a high pressure liquid chromatography (HPLC) e2695 Waters Associates (Milford, MA, USA) equipped with a column The Xterra MS C18 5 µm, 4.6 x 250 mm. The two mobile phases were phosphate buffer containing monopotassium dihydrogen phosphate (KH_2PO_4) (0.05 molar; pH 4.2) in HPLC water and acetonitrile. All mobile phase is HPLC grade obtained from Merck, Darmstadt, Germany. Midazolam and morphine was assayed separately at the wavelength of maximum absorbance, that is 240 nm. 10 µL samples were injected into the HPLC system using an auto sampler injector SM 7 at a solvent flow rate of 1 mL/minute, and using a 2489 UV/Vis detector. Concentration remains >±90% is justified as chemically compatible. A reduction of concentration >±10% is unacceptable

2.4 Validation

Validation was confirmed on linearity, accuracy, and precision (see Table 1.1), Precision was determined by measuring the concentrations of on day 1, 3 and 7 in five replication. Table 1 demonstrates that the accuracy (by both peak height and area) ranges within 95–105%, and the intra- and inter-day coefficients of variation were less than 5% on the five replicate assays (9). Both peak height and peak area have similar acceptable ranges of linearity, accuracy and precision. The validation showed that the method is applicable to measure concentration of midazolam and morphine.

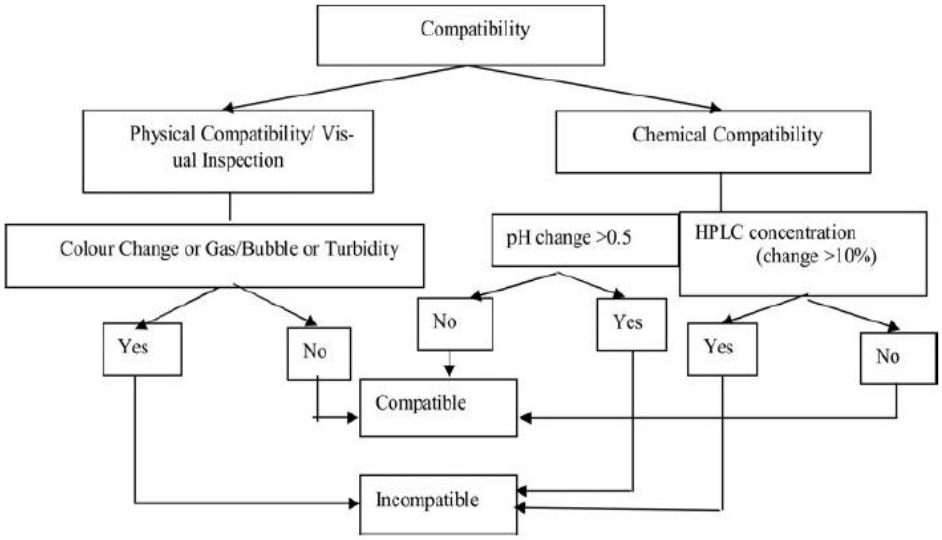

Fig. 1 Criteria of incompatibility [10,11]

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Table 1. Validation on accuracy and precision in HPLC system

Sample Added Concentration	Initial Concentration	% Accuracy (Cv)	% RSD Intra-day	% RSD Inter-day
Midazolam 0.58 mg/mL	0.59 mg/mL (101.72%)	100.70 (1.59)	1.54	1.09
Morphine 96 µg/mL	96.95 µg/mL (100.99%)	101.10 (0.29)	1.37	2.55

The current investigation showed that morphine and midazolan were physically compatible during 168 hours; there was no turbidity, discoloration, effervescence or precipitation throughout the seven days of observation. Therefore, it is important to take into account any chemical changes. Further inspection including an examination of pH showed that pH changes were also in range of ± <0.5. In addition, the percentage degradation of midazolam and morphine were within acceptable ranges of <90% during the seven days' observation.

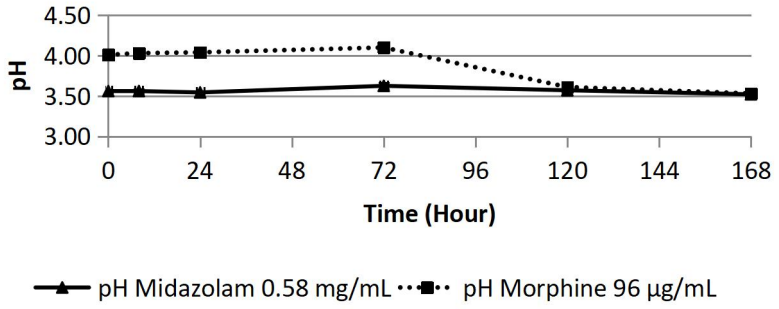

Fig 2. The pH of Midazolam and morphine up tp 168 hours

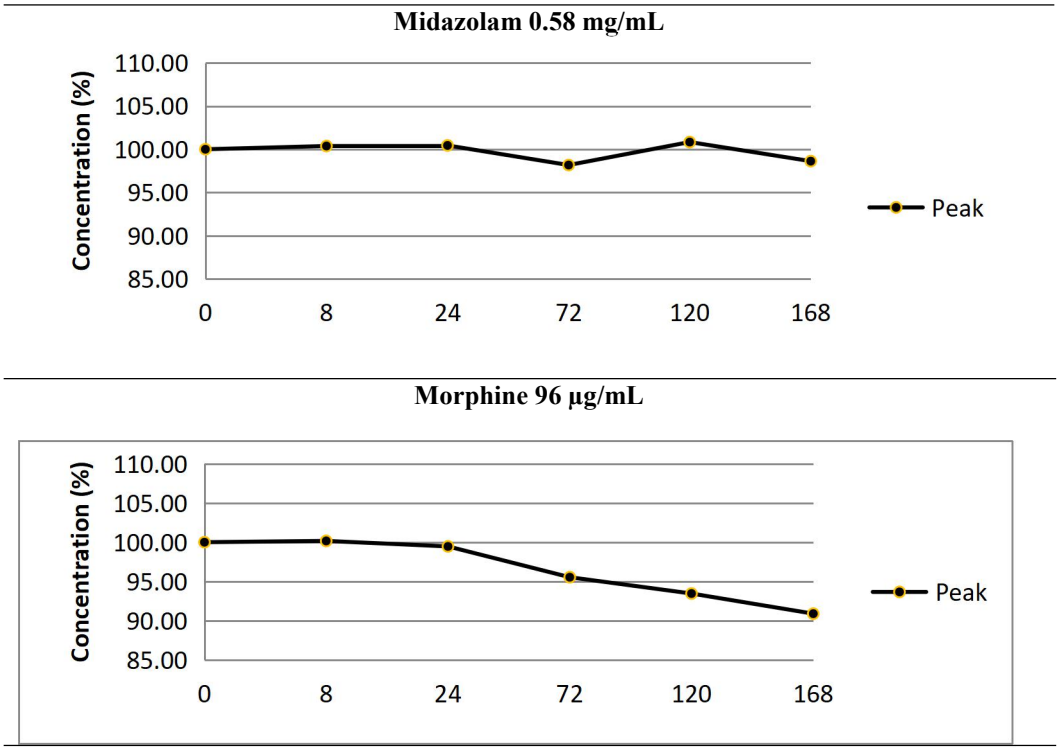

Fig 3. The concentration changes of Midazolam and morphine

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4. Discussion

The current findings regarding the stability of midazolam and morphine are in accordance with those of other scholars (12, 13) in which midazolam and morphine were found to retain 90% concentration for 20 days and seven days, respectively. The extrapolation results were that 90% concentration of midazolam remained for 20 days, while 90% concentration of morphine was demonstrated as being present at seven days.

Midazolam seems to be stable in 5% glucose solution despite ambient temperature and light exposure. This finding means that the reconstitution of midazolam in 5% glucose solution, as prepared in PICU Sardjito, is safe with regard to compatibility and stability. This duration can even be prolonged up to seven days. This study's finding was similar to those of Karlage [12] and de Diego [14] in which they found that midazolam HCl at 1 mg/mL and 0.5 mg/mL was stable in 5% glucose solution under room temperature and light exposure for 20 days and 14 days, respectively. Although midazolam is a light-sensitive drug, it is sufficiently stable under hospital conditions. This finding supported that of Karlage [12] who identified that midazolam retained the same concentration during 27 days' storage under different conditions (refrigerator/room temperature, clear/amber packaging).

Even though past studies have mostly suggested NS and WFI for reconstitution of morphine, the current study has proven that 5% glucose solution can be an alternative vehicle. In addition, this finding confirms that morphine is not only stable while under protection from light, as in the study conducted by Vermeire and Remo[8], but also when exposed to light. Furthermore, the current study has confirmed Strong's [13] study in which morphine sulphate was found to be stable for a week under ambient temperature and light exposure: light was thought to accelerate the decomposition from twofold to sixfold. Even though temperature and light increase degradation, Vermiere proposed that pH and oxygen are more important factors in affecting stability.

remove any reference to colour in the illustration and text. In addition, some colour figures will degrade or suffer loss of information when converted to black and white, and this should be taken into account when preparing them.

This research has attempted to imitate the routine work in hospitals, the circumstances and the materials were applied according to hospital conditions ; therefore this result would be applicable only in the similar condition.

5. Conclusion

This research sums that midazolam 0,58 mg/mL and morphine 0,96 µg/mL in 5% glucose are physically and chemically compatible up to 168 hours. However, morphine concentration decreased considerably since 72 hours to 168 hours (95% to 90%) .

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