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Stability consideration in extemporaneous omeprazole suspension

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Abstract

Omeprazole (OMP) is a drug used to treat gastroesophageal reflux disease (GERD). Pharmacists also use commercially available capsules of OMP to prepare extemporaneous suspensions for juvenile and geriatric patients and other patients who are unable to swallow capsules. The stability of extemporaneous preparations should be determined on a regular basis in hospital settings. The aim of this study was to evaluate the effect of temperature on the stability of an OMP extemporaneous suspension. A 2 mg/mL OMP extemporaneous suspension was prepared and transferred into plastic bottles for storage at 4±3 °C (refrigerated), 25±5 °C (room temperature) and 45±5 °C (accelerated temperature). After 0, 7, 14, 28, 60, and 90 days, samples were evaluated for appearance and OMP content was determined by high-performance liquid chromatography (HPLC). The percentage deterioration in OMP content was determined for chemical stability. The color of the OMP solutions changed from brownish to dark purple after 7 days at all three storage temperatures. The OMP content of the extemporaneous solutions remained above 90% for 28 days at the refrigerated temperature (90.16±1.70%) and for 7 days at room temperature (92.09±3.44%). There was no OMP detected after day 0 at the accelerated temperature. To conclude, OMP extemporaneous suspensions can be safely stored at 4±3 °C for 28 days. These results will provide hospital pharmacists with stability data to use as a guideline for appropriate storage conditions of OMP extemporaneous preparations.

Keywords: Extemporaneous suspension, Stability, Omeprazole, Physicochemical properties

1. Introduction

Omeprazole (OMP) is a proton pump inhibitor (PPI) that comes in the form of a delayed-release capsule of enteric-coated granules to prevent acid degradation [1]. OMP is a prodrug that is only converted to its active form in the parietal cell, which is the site of action. OMP is used to treat peptic ulcer disease, gastrointestinal reflux, and *Helicobacter pylori* infection [2-3]. The administration of OMP is difficult in neonates, infants, the elderly, and those with abnormal esophageal function who are unable to swallow and must rely on nasogastric or gastrostomy tubes to obtain medications. The suggestion for OMP administration to these populations is to open the capsules and mix the granules with mild acidic food or to flush the granules through the nasogastric tube with liquid. Extemporaneous preparation is a popular solution when no commercial type of a medication is available, particularly for the above mentioned patients. An extemporaneous OMP suspension provides an alternative liquid preparation to capsules. However, the stability of OMP in extemporaneous suspensions prepared at the hospital remains unclear. To meet the requirements of the International Council for Harmonisation (ICH), stability testing for new dosage forms (Q1C) and evaluation for stability data (Q3E) should be carried out, including the toxicity of degradation products, for safety and efficacy [4-5]. In general, factors such pH, heat, and moisture can degrade drug substances and drug products. A previous study found an extemporaneous suspension of OMP prepared for

children from OMP capsules was stable in a refrigerator (2-8 °C) for 30 days, but unstable at room temperature [6]. Further more, an OMP oral suspension prepared in a Humco Flavor Sweet Sugar Free vehicle was stable for at least 90 days at refrigerated conditions [7], and an OMP suspension prepared using a commercial kit was stable for 30 days in a refrigerator [8].

The objective of this study was to evaluate the physicochemical stability of an OMP extemporaneous suspension over, 90 days under 3 temperature conditions: refrigerated, room temperature and accelerated temperature.

2. Materials and methods

Reagents: omeprazole capsules were purchased in Thailand from a Berlin-based pharmaceutical company, sodium hydroxide, monobasic sodium phosphate, acetonitrile, and other analytical-grade chemicals and reagents were purchased locally and met the Thai Pharmacopeia requirements.

Materials: Shimadzu high-performance liquid chromatography (HPLC) system, UV-visible spectrophotometer (Shimadzu 1800, Japan), Erlenmeyer flasks, plastic bottles, microtubes.

2.1 Determination of λ_{max}

To assess the λ_{max}, OMP was first dissolved in methanol, then diluted with distilled water and scanned by using an ultraviolet (UV) visible spectrophotometer (Shimadzu 1800, Japan) in the range of wavelengths 200-400 nm.

2.2 Preparation of omeprazole suspension

OMP suspension was prepared by opening sixty capsules of OMP into a mortar and grinding them and then transferring the powder into a 1000 mL Erlenmeyer flask. The pH was adjusted to 11 with 200 mL sodium hydroide solution to get a final concentration of 2 mg/mL OMP. The blend was magnetically stirred for 30 min. Subsequently, 30 mL of suspension was drawn into 50 mL aluminum foil covered plastic bottles and stored in the refrigerator (4±3 °C), at room temperature (25±5 °C), and at accelerated temperature (45±5 °C). At the specific times of 0, 7, 14, 28, 60, and 90 days, samples were evaluated on physical properties (color) and chemical characteristics. For the remaining content of OMP, each bottle was shaken to maintain uniform dispersion and homogeneity of the suspension. An aliquot from each bottle was diluted to 50 µg/mL and placed into microtubes and vortexed for one minute. A 0.5 mL sample was withdrawn from each microtube and transferred to a vial of HPLC auto-injector for analysis. All samples in each condition were analyzed in triplicate [9].

2.3 High-performance liquid chromatography (HPLC)

HPLC was used to determine the concentration of omeprazole [10]. OMP is detected at a wavelength of 285 nm. Analytical-grade acetonitrile/water (45:55 v/v) was used as the mobile phase and the temperature was 35 °C. Using 1 M monobasic sodium phosphate salt, change the pH to 7.5 and injection volume of 150 µL and flow rate of 1 mL/min with column C18 particle diameter 3.5 µM. An analytical-grade omeprazole stock solution was prepared as a regular curve per day. Samples were diluted with a 45:55 solution of acetonitrile and water, diluted to a concentration of 1-5 g/mL. The r^2 was calculated for the relationship between peak area under the concentration-time curve (AUC) and the OMP concentration remaining was determined as a percentage of total drug concentration.

A standard curve was prepared by serially diluting the stock solution with the mobile phase. Stock solutions were made from standard grade reagents. Concentration for calibration was 0, 50, 100, 150 and 200 µL/mL for a linear plot of omeprazole over the range of 0 to 200 µL/mL [9].

2.4 Stability study

Each preparation's percentage of remaining drug at a given time was measured. Graphs were used to test the triplicate samples. The degradation rate profile of OMP suspension was calculated, as well as the approximate shelf life (90-110% Label Amount).

2.5 Appearance test

Visual examination was used to evaluate the color of the samples in each condition.

2.6 Data analysis

Suspensions with the content of OMP in the acceptable range from 90 to 110% were considered stable.

3. Results and discussion

3.1 Results

The color of the suspensions changed from brownish to dark purple after seven days under all conditions. The remaining content of OMP for 90 days at the 3 different storage conditions is expressed as mean percentage of initial OMP concentration, as shown in Table 1. Little degradation was observed in OMP content of suspensions stored at refrigerated temperature up to 28 days, but at room temperature, OMP content remained over 90% for only 7 days. At accelerated temperature, there was no OMP detected after the initial day.

3.2 Discussion

Omeprazole is a drug that has a high rate of usage in hospitals, but its liquid form is unavailable in Thailand. As the drug is not available in liquid form, patients need to crush tablets or open capsules to adjust the dose, and they need to mix with juice or milk to take the drug in liquid form. This action can cause problems for patients with over dosage or lower dosage. In this study, the an extemporaneous suspension of OMP 2mg/mL was produced from commercially available capsules. The suspension was stored under 3 different temperatures; at room temperature (25±5 °C), at refrigerated temperature (4±3 °C), and at accelerated temperature (45±5 °C), for 90 days.

Color is the most important aspect of appearance as it is the first impression to patients. Changes in color can indicate the reaction of medicine and the presence of degraded compounds. In this study, the color changed from from brownish to dark purple after seven days under all storage conditions, indicating the presence of the sulfone derivative degradation compound.

Another evaluation of this study was to investigate the chemical stability of OMP under these storage conditions. The acceptable range for a suspension formulation is 90 to 110% of the label amount of drug [4]. The initial concentration of all OMP extemporaneous suspensions examined in this study was equal to 100% at commencement. Under refrigerated conditions, the content of OMP remained above 90% for up 28 days. At room temperature conditions, OMP content remained above 90% for 10 days. For accelerated temperature conditions, the remaining content of OMP was under the limit of detection by HPLC after the initial measurement on day zero. At day 90, the content of OMP was depleted by 32% under refrigeration and by 86.49% at room temperature. The decomposition of the drug was rapid, resulting in separated peaks on HPLC. From the disappearance of the OMP peak, we can assume that the OMP preparation was not stable at accelerated temperature (Figure 1). Previously described the effect of enteric-coated polymers dispersed in water on the stability of OMP. The enteric-coated polymer structure contains phthalate moieties that may cause hydrolysis and decomposition of OMP. In aqueous solutions, the amount of free acid in some types of polymers can deteriorate the proton pump inhibitors (PPIs) [11]. The method used in this study was based on a previous study [12]. The chemical stability of OMP in extemporaneous solutions for 28 days at refrigerated temperature in this study is concordant with the previous study [9]. This result provides useful information about the duration of OMP drug stability that will allow pharmacists to prepare extemporaneous solutions and store them safely for future usage. According to the results, storage in a refrigerator is the best condition for OMP suspension among the three different temperatures, as this condition kept the OMP suspension's physical and chemical characteristic stable for 28 days. A previous study also showed that an OMP suspension was chemically stable under refrigerated condition, but the patients complained about the unpleaant taste of the suspension. Since added flavoring may reduce the stability of OMP, it has been recommend that OMP should be mixed with milk [13]. The results of this study will be useful for pharmacists to prepare the extemporaneous suspension of OMP. The stability of OMP suspension must be evaluated in other vehicles, as the context of drug-vehicle selection in each hospital is different. Therefore, to find a suitable vehicle, pharmacists need to review literature about the vehicle that increases the stability of each type of drug.

Table 1 The stability of OMP suspensions stored at different temperatures (n=3).

Time (Days)	Percentage of drug remaining (Mean±SD)		
	Refrigerator temperature (4±3 °C)	Room temperature (25±5 °C)	Accelerated Condition (45±5 °C)
0	100.00±2.24	100.00±0.88	100.00±1.19
7	95.16±1.70	92.09±3.44	NQ
14	93.06±1.28	93.06±1.28	NQ
28	90.16±1.70	61.94±7.23	NQ
60	81.21±1.77	36.45±5.79	NQ
90	68.00±4.63	13.51±2.34	NQ

Note: NQ is none quantified.

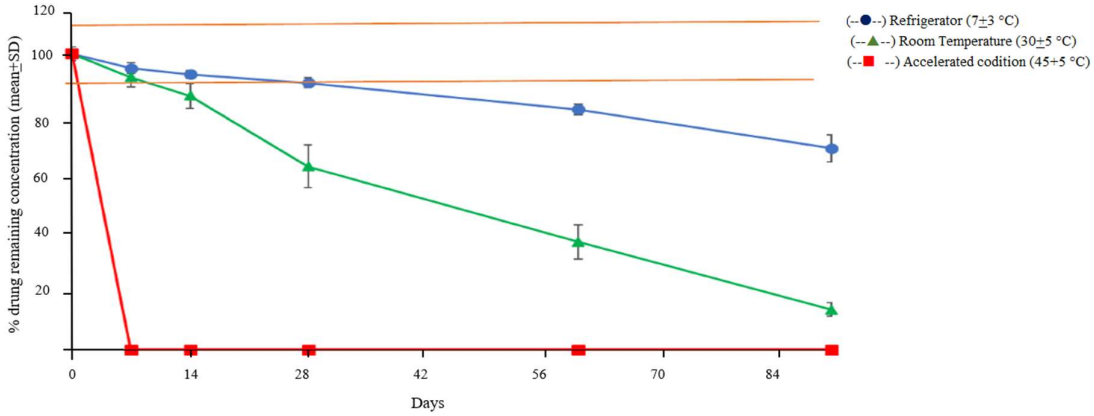

Figure 1 The percentage of a remaining drug profile of extemporaneous omeprazole suspension at refrigerator.

4. Conclusion

An extemporaneous OMP suspension at therapeutic dose (2 mg/mL) was stable in a refrigerator (4±3 °C) for 28 days and at room temperature (25±5 °C) for 10 days.

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6. Conflicts of interest

The authors declare that they have no competing financial interests that could have appeared to influence the work reported in this paper.

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