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RESEARCH ARTICLE

Stability of omeprazole in a commercial calcium carbonate based oral suspension at 2, 5 and 10 mg/mL stored under refrigeration (4°C) for 70 days

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Abstract

Background: Omeprazole is a commonly prescribed proton pump inhibitor that acts to reduce gastric acid secretion. Liquid suspensions are preferred for paediatrics or patients with difficulty swallowing, however, are unstable.
Aim: This study reports on the stability of USP-grade omeprazole, raw powder at 2, 5 and 10 mg/mL dosages suspended in Oral Mix Dry Alka SF (OMSF) stored at 4°C for 70 days.
Method: The omeprazole concentration in the suspensions were determined at the time of preparation and at 7, 14, 28, 42, 56 and 70 days by high performance liquid chromatography with photodiode array detection (HPLC-PDA). The pH, homogeneity, colour, odour, and microbial levels were also determined.
Results: All the preparations are stable at 4°C for 70 days, with omeprazole concentration remaining within ±10% of the initial concentration. The pH showed a gradual decline from 9.0 to 7.7 over the study which is an acceptable change. The preparations passed microbial testing up to 70 days.
Conclusion: The 70 days stability achieved in OMSF far exceeds the 28 day beyond-use-date recommended by the Australian Pharmaceutical Formulary. The OMSF base provides compounding pharmacists with a convenient method to prepare omeprazole suspensions over a wide range of concentrations with extended dating, providing added convenience for the consumer and pharmacists.

Keywords: omeprazole, stability, suspension vehicle, oral-mix, proton pump inhibitor.

INTRODUCTION

Omeprazole (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridinyl) methyl]sulphinyl]-1H-benzimidazol) is a proton pump inhibitor that acts to reduce gastric acid secretion.[1] It is an important medication as 17% of adults in Australia are prescribed proton pump inhibitors (PPIs)[2] and it is increasingly being prescribed for infants. Omeprazole is commonly used to treat acid-related disorders such as gastroesophageal reflux disease, peptic ulcer, and Zollinger-Ellison syndrome. Although lacking supporting evidence, PPIs are also prescribed for infants with general symptoms such as irritability and crying (or colic) on the assumption that reflux might be the cause.[3]

Omeprazole is converted at stomach acid pH (1.5–3.5) to a cyclic reactive sulfonamide[4] which inhibits gastric secretion by selectively and irreversibly inhibiting stomach parietal cells H^+, K^+-ATpase.[1] However, the reactive form is also unstable and degrades rapidly in acidic solution.[5] One study reported that about 70% is degraded at pH 3 but did not state the timeframe for the degradation.[6] The study also reported heat degradation data stating only 14% degradation when stored for at 80°C for 45 min.

Commercial oral dosage forms including capsule release enteric-coated granules or enteric-coated tablets have a typical shelf life of 1–2 years. These dosage forms, however, are unsuitable for paediatric patients or those with swallowing difficulties for whom homogenous flavoured liquid suspensions would be suitable.

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To improve pH and temperature stability, preparations are typically prepared in sodium bicarbonate buffered solutions and kept refrigerated. A recent study was able to develop a formulation that achieved stability of omeprazole powder for 90 days, under refrigeration.[7] Preparing the suspension base from several ingredients is inconvenient and not widely practised clinically. Commercially pre-prepared bases are more commonly used and are generally preferred for their ease of use and improved palatability.

If a commercial base is used, suspensions of different concentrations can be easily prepared. There are limited studies on the stability of omeprazole at various concentrations. Burnett *et al*. examined the stability of 0.6–4.0 mg/mL sodium bicarbonate buffered omeprazole suspensions at room temperature and found that stability was concentration dependent with relative losses decreasing with increasing omeprazole concentration.[8] This observation was explained by the higher concentration of sodium bicarbonate in the more concentrated omeprazole preparation thereby stabilising it. Omeprazole has been reported to be most stable at pH 11 while below pH 7.8 there is rapid decomposition.[5] The kinetics of decomposition follow zero-order kinetics meaning that the rate of decomposition is constant over time.[9,10]

Instead of sodium bicarbonate Oral Mix Dry Alka, SF suspending vehicle (OMSF) contains calcium carbonate as the pH neutralisation agent.[11] Calcium carbonate's neutralising ability and greater palatability makes OMSF a promising oral base for acid-labile drugs. OMSF (cherry flavoured) has a pH of 9 and is dye-free. Omitting ingredients such as dyes helps to alleviate concerns that some in the paediatric population may have sensitivities to food colouring.

The aim of this study was to report on the chemical and microbiological stability of omeprazole sourced as the USP (United States Pharmacopeial) grade raw powder at three concentrations (2, 5 and 10 mg/mL), stored at 4°C in amber polypropylene (low actinic) bottles due to the reported light sensitivity of omeprazole.[6]

METHODS

Chemicals and Reagents

USP-grade omeprazole raw powder for preparing the test suspensions was supplied by Medisca Inc. (Sydney, Australia). Omeprazole reference standard material was purchased from The United States Pharmacopeial Convention (Rockville, USA). The pharmaceutical grade Oral Mix Dry Alka, SF suspending vehicle (OMSF) was supplied by Medisca Inc. (Quebec, Canada). Monobasic sodium phosphate was purchased from Sigma Aldrich (Castle Hill, Australia). HPLC grade acetonitrile was from Chem-Supply (Gillman, Australia). Purified water (>18 MΩ·cm) was obtained from a Merck Millipore Direct 8 MilliQ system (Bayswater, Australia).

Equipment and Chromatographic Conditions

A Shimadzu Prominence HPLC system with degassing unit (DGU-20A5), autosampler (SIL-20AC) coupled to a PDA detector (SPD-M20A) (Rydalmere, Australia) was used for the analysis. Chromatographic separation was achieved on a Phenomenex Kinetex 5 μm EVO C18 100 Å, 250 × 4.6 mm column (Lane Cove, Australia). The instrument was controlled using Shimadzu LabSolutions software version 5.57 SP1.

Mobile phase A was 50 mM monobasic sodium phosphate buffer (pH 8.5) in purified water and mobile phase B, LC grade acetonitrile. The mobile phase of aqueous acetonitrile (1:4, acetonitrile:water) was run isocratically at a flow rate of 1 mL/min. The injection volume was 30 μL and run time 10 min. The column oven temperature was set at 30°C. The mobile phase was used as the solvent to prepare the standards and samples. Chromatograms were visualised at 302 nm.

The pH of samples was measured with a Schott Lab 850 pH meter (Mainz, Germany).

HPLC-PDA Analysis of Omeprazole

The analytical method was characterised for its performance in determining omeprazole concentration in the matrices of interest. This was achieved by checking if the omeprazole peak was resolved from those of the suspension vehicle components and forced degradation products produced by exposing the OMSF (blank and containing 2 mg/mL omeprazole) to heat, acidic, basic, and oxidising chemical conditions (70°C, 1 M hydrochloric acid, 1 M sodium hydroxide and 30% *v/v* hydrogen peroxide, respectively; 1 mL each added to 1 mL sample) for 30 min. The acidified and basified samples were neutralised with sodium hydroxide and hydrochloric acid, respectively, before analysis. The omeprazole concentration was adjusted with the mobile phase (diluted 1:50) prior to analysis. Calibration curve linearity was determined over the 1.0–100.0 μg/mL range using seven dilutions of omeprazole working standards. The working standards were prepared by diluting the 100 μg/mL omeprazole reference standard stock in the mobile phase prepared on day of use. To determine the omeprazole peak area and retention time precision, a 50 μg/mL standard solution was injected six times, this was repeated as a precision check at each time point. The relative standard deviation (RSD) of both the peak area and retention time

were determined and deemed acceptable if the RSD was ≤ 2.0%. The calibration curve was acceptable if the coefficient of determination, r^2 was ≥ 0.999. Blank injections of OMSF were made to check for interfering peaks. Overlay of the UV spectrum of the omeprazole peak obtained from the standard and sample solutions was performed to check for peak purity.

Intraday precision of the method was determined using omeprazole suspensions prepared from the raw powder in OMSF to a concentration of 2 mg/mL. Six samples of each preparation were diluted (1:1000) in the mobile phase and injected in duplicate. For interday precision, omeprazole preparations of each suspension were assayed under identical conditions but on subsequent days.

At the initial and predetermined time points, the omeprazole peak area was measured for each injection and averaged for each sample. Concentration was reported as the mean and relative standard deviation (RSD). The stability of omeprazole raw USP powder in OMSF suspending vehicle packaged in amber bottles and stored under refrigeration was determined by measuring the concentration of omeprazole at each time point and calculated as a percentage of the initial concentration.

Sample Preparation

Oral suspensions of omeprazole (2, 5 and 10 mg/mL) were prepared from the USP-grade powder. Three batches at three concentrations were prepared from preweighed (6.35 g for 2 mg/mL, and 6.75 g for 5 and 10 mg/mL) OMSF powder in 100 mL graduated polypropylene (low actinic) bottles. To this 200, 500 and 1000 mg of omeprazole raw powder (purity 99.6%) was added, followed by approximately 60 mL water and shaken vigorously by hand for not less than 60 s until the suspension appeared uniform. Water was then added to the 100 mL mark. The press-in adapter was then inserted. This adapter is a circular stopper-like device with a central hole and fits securely over the bottle, allowing a user to easily draw liquid with an oral dispenser, ensuring accurate dosing while avoiding spills and helping to minimise contamination of the preparation. The adapter fits flush with the bottle opening so that the original cap can be placed on the bottle. The suspensions were stored in a temperature-controlled refrigerator (Model TLR-1150-3-SD; Thermoline Scientific, NSW, Australia) set at 4 ± 2°C and 60 ± 5%RH.

Stability Protocol

Samples were tested at the time of preparation after one week and then every 2nd week for 10 weeks (70 days). The bottles were shaken vigorously by hand for about 30 s before sampling by a glass pipette. The contents were inspected for colour, odour and homogeneity and the pH measured.

On day 7, 14, 28, 42, 56 and 70 days, aliquots from the bottles were sampled in triplicate. After dilution with LC mobile phase to an expected concentration of 50 μg/mL the samples were analysed in triplicate by HPLC-PDA.

The omeprazole samples stored at 4°C were analysed at each indicated time point. The acceptance criteria are for the analyte to remain within 90–110% of the initial concentration, and negligible change in visual appearance, colour, and odour.

Microbiological Stability

To assess the microbial status of the preparation, additional testing was conducted by CED Analytical Labs. Triplicate batches of Omeprazole OMSF suspensions (2 mg/mL) were prepared separately, using the same procedure as described previously. The samples for all eight time points were drawn from the same bottle using the press-in bottle adaptor. Microbiological status was assessed through Total Aerobic Microbial Count (TAMC), Total Yeast and Mould Count (TYMC) and *E. coli* testing through rapid microbiological methods that were validated as equivalent to USP and with acceptance criteria set by the USP <1111>.[12] This procedure uses an optical instrument system (BioLumix; Neogen Corporation, Lansing, MI) that detects microorganisms based on a function of colour or fluorescence. Samples are diluted according to the specification in test vials with defined growth media, and detection recorded during a 30 h, 35°C incubation period for TAMC, and a 48 h, 28°C incubation period for TYMC. Suitability testing was carried out on the compounded preparation to ensure that microbial activity can be detected by microbial inoculation (Procedure M500; CED Analytical Labs, Irving, TX).

RESULTS

Using the chromatographic conditions described and with the chromatograms visualised at 302 nm, the HPLC-PDA method gave a sharp omeprazole peak (retention time 6.4 min, peak width 0.8 min) which was well resolved from peaks from the suspension vehicles and degradation products.

Forced degradation studies of omeprazole prepared in OMSF showed little change in concentration for the heat- and alkaline-treated samples compared to the

untreated control samples. However, for the acid- and oxidant-treated samples, omeprazole concentration decreased by 98% and 100%, respectively. The acid-treated samples had multiple peaks eluting before the 6.4 min omeprazole peak followed by two small broad peaks. The omeprazole peak decreased significantly but remained well resolved. Chromatograms for the degradation study are shown in Figure 1 (chromatograms visualised at 302 nm).

The calibration curve was linear ($r^2 > 0.9998$) between 1 and 100 μg/mL. The RSD for the three samples analysed was 0.29%. The interday RSD was 0.45% (determined from the difference between the average mean obtained for each day over 2 days).

Table 1 presents the mean percentages of omeprazole in OMSF remaining from the original concentration at the predetermined time points along with their associated RSD determined from triplicate preparations. There was a steady drop by about 4% from 0–7 days and then all dosage forms remained stable thereafter. All samples had concentrations within the 91–98% range of the initial concentration thereby lying within the specified 90-110% range to be considered chemically stable.

All samples maintained their initial off-white colour and opaque appearance with no observable evidence of caking. For all the omeprazole concentrations studied, a gradual but minimal pH decline was observed (from 9.0–7.7) (Figure 2).

On each testing day, the TAMC and TYMC values met the acceptance criteria and *E. coli* was not detected for all samples as seen in the Table 1. The OMSF

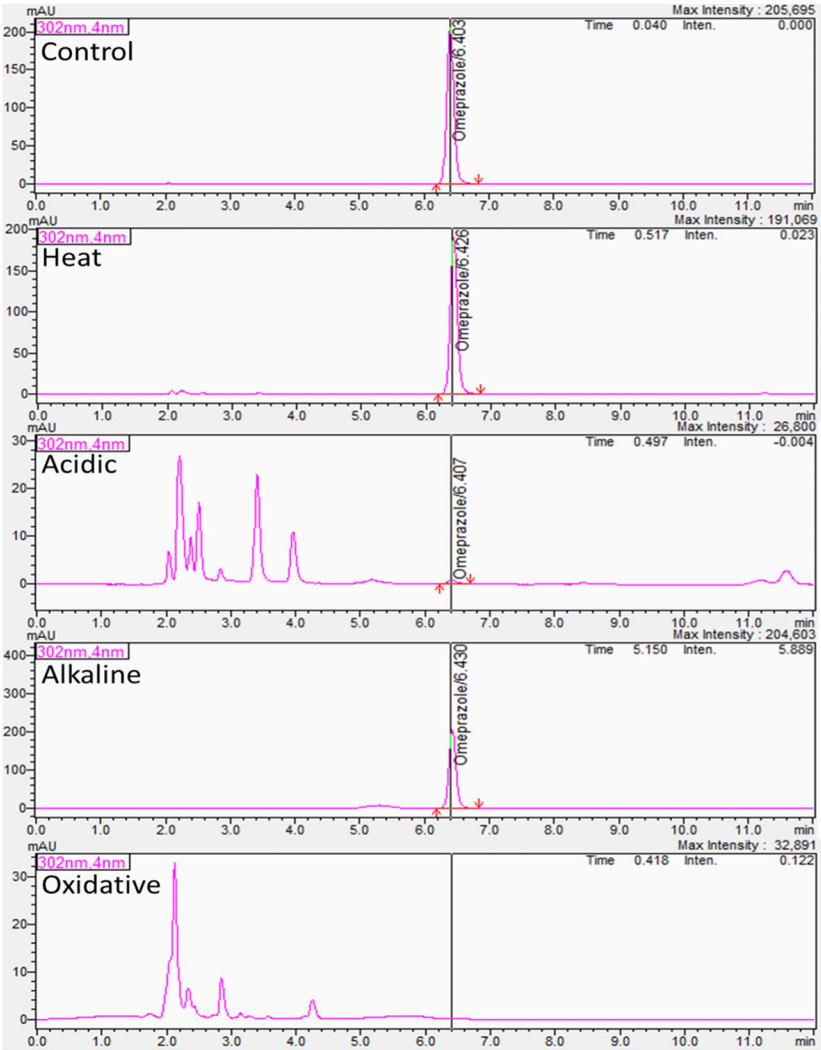

Figure 1 Sample chromatogram of omeprazole in Oral Mix Alka Sugar Free, in control, heat treated (70°C), acid treated (1 M hydrochloric acid), alkali treated (1 M sodium hydroxide) and oxidative treated (30% *v/v* hydrogen peroxide).

Table 1 Stability of omeprazole in Oral Mix Alka Sugar Free over 70 days

		0 day	7 days	14 days	28 days	42 days	56 days	70 days
2 mg/mL omeprazole	pH	9.02	8.82	8.5	8.51	8.52	8.07	7.77
	Colour	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)
	Assay mg/mL	2.10	2.02	2.01	2.02	2.00	1.97	2.04
	%RSD	0.56	1.07	1.61	0.23	0.91	0.70	2.51
	Percentage of starting concentration	100%	96%	96%	96%	95%	94%	97%
	TYMC (cfu/g)	<100	<100	<100	<100	<100	<100	<100
	TAMC (cfu/g)	<100	<100	<100	<100	<100	<100	<100
	E. coli	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
5 mg/mL omeprazole	pH	9.04	8.67	8.61	8.57	8.50	7.95	7.90
	Colour	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)
	Assay mg/mL	5.24	5.05	5.00	5.04	5.05	5.01	4.81
	%RSD	0.59	0.69	0.47	0.19	0.27	0.87	1.33
	Percentage of starting concentration	100%	96%	95%	96%	96%	96%	92%
	TYMC (cfu/g)	<100	<100	<100	<100	<100	<100	<100
	TAMC (cfu/g)	<100	<100	<100	<100	<100	<100	<100
	E. coli	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
10 mg/mL omeprazole	pH	9.03	8.76	8.74	8.75	8.27	8.03	7.84
	Colour	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)	Off white (Pantone p 7-1 C)
	Assay mg/mL	10.62	10.22	10.05	10.08	10.22	10.18	9.65
	%RSD	1.78	2.14	2.30	1.38	1.77	0.43	2.67
	Percentage of starting concentration	100%	96%	95%	95%	96%	96%	91%
	TYMC (cfu/g)	<100	<100	<100	<100	<100	<100	<100
	TAMC (cfu/g)	<100	<100	<100	<100	<100	<100	<100
	E. coli	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected

RSD = relative standard deviation; TAMC = total aerobic microbial count; TYMC = total yeast and microbial count.

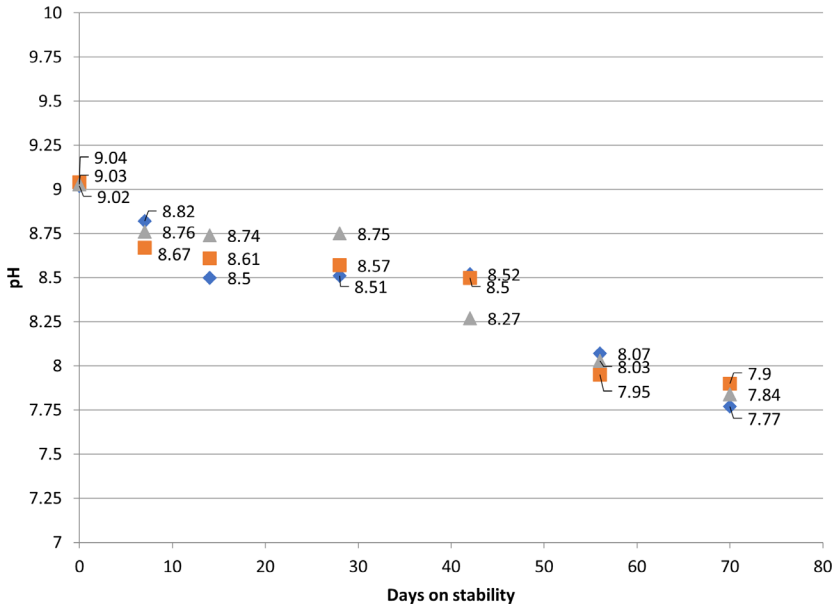

Figure 2 pH of omeprazole 2 mg/mL (blue ♦) 5 mg/mL (orange ■) and 10 mg/mL (grey ▲) in Oral Mix Alka Sugar Free at 4°C.

suspension remained microbiologically stable throughout the 70-day testing period.

DISCUSSION

The method was determined to be stability indicating by a forced degradation study. As seen in Figure 1, acid and oxidation cause significant degradation, however the degradants were well resolved from the omeprazole peak. There have been studies on the products from acid degradation of omeprazole.[13,14] One of the proposed degradation structures show fragmentation of the parent molecule where the S-C bond linking the two ring structures is cleaved to give two smaller molecules.[14] Molecular rearrangements also occur as well as the formation of dimers with one to three S-atoms in the bridge, approximately doubling the molecular weight probably accounting for the longer retention time peaks. Some of the products reported to be formed are 5-methoxy-2-benzimidazole-2-thiol, omeprazole sulphide and omeprazole desmethoxy.[15]

All the dosages maintained their omeprazole concentration within 90–110% of initial concentration. Burnett *et al*. studied the stability of omeprazole 0.6–4 mg/mL in sodium bicarbonate buffered suspensions at room temperature and found that stability was concentration dependent, however there was no significant difference under refrigeration.[8] Our investigation found that from 2–10 mg/mL omeprazole in OMSF kept under refrigeration, there was no concentration-dependent difference in stability.

All suspensions were found to be stable for 70 days under refrigeration. The USP gave a beyond-use date of 45 days under refrigeration[12] (until the monograph was withdrawn in April 2019), but up to 90 days has been achieved with modifications to the suspension base.[7] The Pharmaceutical Society of Australia currently recommends 28 days.[16] The OMSF pre-formulated bases offers a simple and validated base to extend the stability of omeprazole in suspension. Pre-formulated bases reduce the possibility of formulation error and simplify the preparation process for compounding pharmacists, hence commercial pre-prepared bases are widely used in practice.

Omeprazole degrades rapidly in an acidic solution.[5] Previously sodium bicarbonate has been used as buffer, OMSF contains calcium carbonate as the pH neutralisation agent. While both have fast onset of action, calcium carbonate has a prolonged duration of action compared to sodium bicarbonate.[11] The difference in duration of action is likely due to calcium carbonate being far less water soluble than sodium bicarbonate[17] thereby going into solution gradually as it is consumed by acid. It is plausible that other calcium carbonate based oral delivery fluids would achieve similar stability, however further studies are required to support this assumption.

Omeprazole suspensions have been reported to change colour as they degrade. There was no change in colour observed over the 70 days. A study of the

stability of omeprazole in an extemporaneously prepared oral liquid[10] reported that their sample stored at 24°C gradually changed from white to brown but no explanation for this observation was proposed. Their suspensions stored at 5 and −20°C did not change colour.

The forced degradation study showed little loss of omeprazole when heated and when exposed to base but was found to be unstable under oxidising and acidic conditions. This observation is in harmony with other studies on omeprazole stability.[5] Although pH declined over the 70 days, it remained above 7.7. While there is a study claiming that below pH 7.8 decomposition is very fast,[10] our observations do not bear this out with stability still observed at pH 7.7. Experimental conditions, however, are different – our omeprazole was dispersed in OMSF while the quoted study on pH stability used omeprazole in phosphate buffer. There is a study of omeprazole hydrolysis in the aquatic environment reporting that the drug is stable at pH 7.0 and higher.[18]

The elevated alkaline pH may also inhibit microbial growth. As the pH approaches neutral this action may be compromised. Change in appearance, colour, and odour may all indicate the microbial growth but monitoring these alone may be insufficient to ensure microbial safety. All samples showed no change in colour, odour, or appearance over the 70 days. In addition, the TYMC and TAMC remained within acceptable levels over the 70 days and *E. coli* remained at undetectable levels.

CONCLUSION

The 2, 5 and 10 mg/mL omeprazole suspensions were physically and chemically stable for up to 70 days. There was no concentration-dependent difference in stability. Validated microbiological testing showed that the preparation remained microbiologically stable over the study period. An extended beyond-use-date of 70 days can be assigned to a bracketed range of 2–10 mg/mL omeprazole compounded with Oral Mix Dry Alka, SF when stored in PP (low actinic) bottles at 4°C and is well above the Pharmaceutical Society of Australia recommended 28 days in the absence of stability data.

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CONFLICTS OF INTEREST STATEMENT

As a medical research institute, NICM Health Research Institute receives research grants and donations from foundations, universities, government agencies, individuals, and industry. Sponsors and donors also provide untied funding for work to advance the vision and mission of the Institute. The authors declare no competing financial interests.

AUTHORSHIP STATEMENT

All persons listed as authors have read and given approval for the submission of the manuscript and comply with the journal's authorship policy.

ETHICS STATEMENT

As per *Journal* policy, ethics statements are not required for stability studies not involving human subjects.

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