Bracketed Stability of Extemporaneously Compounded Omeprazole 2, 5 and 10 mg/mL in Oral Mix Dry Alka, SF (Cherry Flavored)

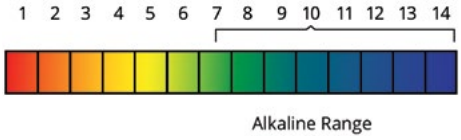
Introduction

Omeprazole is a drug that acts as a proton pump inhibitor (PPI) to suppress gastric acid secretion. It is used in the therapy of ulcers and relief of gastroesophageal reflux disease (GERD)[1]. Omeprazole is commercially available as a delayed-release capsule formulated as enteric-coated granules, which protect the pH-sensitive drug against acid degradation in the stomach[2], but it is not available in liquid dosage form for patients who are not able

to swallow capsules. A common alternative to capsules is to administer the medication in a compounded liquid, buffered with sodium bicarbonate 8.4 %[3]. This sodium bicarbonate 8.4 % solution is not ideal as an oral vehicle as it has a very bitter taste, which may result in non-compliance, particularly in children. The need for an oral liquid preparation with improved palatability and protection of the drug against acid degradation, led to the creation of Oral Mix Dry Alka, SF. Available in cherry and unflavored options, Oral Mix Dry Alka, SF is a convenient powder for re-constitution to form a sweetened, suspending oral vehicle ideal for drugs requiring an alkaline medium. As opposed to sodium bicarbonate, Oral Mix Dry Alka, SF contains calcium carbonate as the pH neutralization agent. While both have a fast onset of action, calcium carbonate has a prolonged duration of action in contrast to sodium bicarbonate[4]. This prolonged duration of action, combined with the increased palatability of Oral Mix Dry Alka, SF provides a promising alterative for acid-labile drugs. The objective of this bracketed study was to examine the physical characteristics and chemical stability of extemporaneously compounded omeprazole suspensions ranging in concentration from 2 to 10 mg/mL in MEDISCA's Oral Mix Dry Alka, SF (Cherry Flavored) following the FDA's guidance on bracketed study design[5].

Method

Triplicate batches of omeprazole suspensions (2, 5 and 10 mg/mL) were prepared using pre-weighed Oral Mix Dry Alka, SF (Cherry Flavored) powder (6.35 g for 2 mg/mL and 6.75 g for 5 and 10 mg/mL; MEDISCA Pharmaceutique Inc, Montreal, Quebec; lot 16F11) in 100 mL amber polypropylene (PP) UV-Resistant (low actinic) bottles (Medisca Pharmaceutique Inc; product no. 6347). Omeprazole USP (200 mg, 500 mg and 1000 mg; MEDISCA Pharmaceutique Inc lot 135446) was mixed into the pre-weighed base, followed by approximately 60 mL of purified water (Millipore Direct 8 MilliQ system, Merck Millipore, Australia). The suspension was shaken vigorously by hand for no less than 60 seconds until uniform. Additional water was added to achieve the final volume of the graduated 100 mL PP bottle and then shaken to form a uniform suspension. A press-in-bottle adapter (33 mm) was then inserted and the bottles were stored at 4 °C with the use of a temperature-controlled refrigerator (Model TLR-1150-3-SD; Thermoline Scientific). Samples were tested in accordance with Trissel's principles on oral extemporaneous formulations using a validated stability-indicating assay. On each study day, all samples were examined for appearance, color, odor, resuspendability and pH (Schott instrument LAB 850, Germany). Omeprazole concentration was then assayed by high-performance liquid chromatography with ultraviolet detection (HPLC-UV). The HPLC system (Shimadzu, Prominence) consisted of a degassing unit (DGU-20A5) and an autosampler (SIL-20AC) coupled to a PDA detector (SPD-M20A) (Shimadzu, Australia). Chromatographic separation was achieved on a Kinetex 5 µm EVO C18 100 Å, 250 x 4.6 mm column (Phenomenex, Australia). The column oven temperature was set at 35 °C. A 50 µL sample loop was used with UV detection at 302 nm, injection volume was set at 5 µL. Mobile phase A consisted of 50 mM monobasic sodium phosphate buffer (pH 8.5, Sigma Aldrich, Australia) in purified water and mobile phase B, LC grade acetonitrile (Chemsupply, Australia). The elution program was set as isocratic 75 % solvent A and 25 % solvent B. The flow rate was 1.0 mL/min. The instrument was controlled using the Shimadzu Labsolutions software version 5.57 SP1 program.



The method was validated with respect to linearity, precision and specificity. Linearity was determined by plotting the peak area against the concentration of omeprazole. The linearity range was determined as 1–100 µg/mL. Omeprazole standards of concentrations 5, 10, 25, 50, 75 and 100 µg/mL were prepared in Oral Mix Dry Alka, SF (Cherry Flavored) and injected in duplicate. A calibration curve was freshly prepared with each analysis and was linear for each assay day. The precision was determined by the analysis of three samples on two consecutive days. Each sample was injected in duplicate with a reported inter-day precision of 0.45 % for omeprazole in Oral Mix Dry Alka, SF (Cherry Flavored).

A forced-degradation study was performed to determine the specificity of the method. Individual omeprazole suspensions in Oral Mix Dry Alka, SF (Cherry Flavored) were subjected to the following conditions along with vortex mixing and incubating for a period of time: exposure to heat (70 °C) for 45 minutes, treatment with 1 M HCl for 45 minutes, treatment with 1 M NaOH for 45 minutes and treatment with hydrogen peroxide 30 % for 45 minutes. Assay and chromatographic profiles for omeprazole under the effects of stressors were obtained after a period of exposure. Additional peaks representing degradation products of omeprazole in these samples were identified by retention time (RT), and were separated from the main omeprazole peak at 6.4 minutes. Additionally, chromatographic studies were conducted on the excipients used in the preparation of the suspension to ensure there were no interfering peaks. The degradation testing, seen in Figure 1, illustrates that the omeprazole is stable under the conditions of alkali and heat, but shows some degradation when subjected to acid and oxidation as per the conditions of the test. The test is used to determine if the method of analysis used is stability-indicating. No peak overlap due to excipient interference or with degradation products was observed; therefore, the method is stability-indicating.

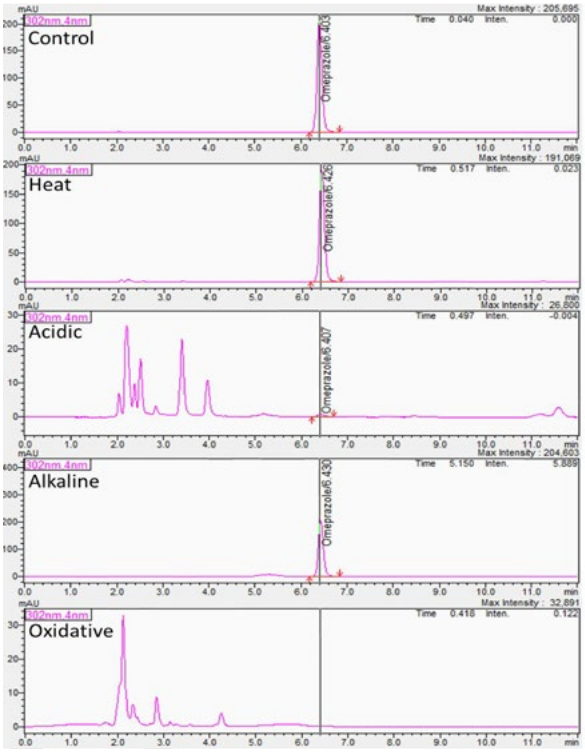


Figure 1. HPLC degradation chromatograms of omeprazole suspension in Oral Mix Dry Alka, SF subject to different stressors

Results

On each study day, all samples were easily resuspended and no odor was observed. The mean omeprazole concentration of 2, 5 and 10 mg/mL at all time points was not less than 90 % of the respective initial concentration as listed in Tables 1, 2 and 3. On day 84, a slight purple tint was observed for all concentrations suggesting decomposition[3] as a result of the decrease in pH. Due to the observed color change, a conservative beyond-use-date of 70 days should be set.

Table 1. Stability of 2 mg/mL Omeprazole Oral Mix Dry Alka, SF (Cherry Flavored) stored in 100 mL amber PP UV-resistant (low actinic) bottles at 4 °C

PARAMETER	DAY						
	0	7	14	28	42	56	70
APPEARANCE	Opaque suspension - normal appearance	✓	✓	✓	✓	✓	✓
COLOR	Off-white	✓	✓	✓	✓	✓	✓
ODOR	Odorless	✓	✓	✓	✓	✓	✓
RESUSPENDABILITY	Easily resuspended – no evidence of caking	✓	✓	✓	✓	✓	✓
pH (7-9)	9.02	8.82	8.50	8.51	8.52	8.07	7.77
ASSAY (mg/mL)	2.10	2.02	2.01	2.02	2.00	1.97	2.04
SD	0.01	0.02	0.03	0.00	0.02	0.01	0.05
95 % CONFIDENCE INTERVAL	0.01	0.02	0.04	0.01	0.02	0.02	0.06
PERCENTAGE OF ORIGINAL CONCENTRATION (%)	100	96.2	95.7	96.2	95.2	93.8	97.1

✓= Conforms to Specification

Table 2. Stability of 5 mg/mL Omeprazole Oral Mix Dry Alka, SF (Cherry Flavored) stored in 100 mL amber PP UV-resistant (low actinic) bottles at 4 °C

PARAMETER	DAY						
	0	7	14	28	42	56	70
APPEARANCE	Opaque suspension - normal appearance	✓	✓	✓	✓	✓	✓
COLOR	Off-white	✓	✓	✓	✓	✓	✓
ODOR	Odorless	✓	✓	✓	✓	✓	✓
RESUSPENDABILITY	Easily resuspended – no evidence of caking	✓	✓	✓	✓	✓	✓
pH (7-9)	9.04	8.67	8.61	8.57	8.50	7.95	7.90
ASSAY (mg/mL)	5.24	5.05	5.00	5.04	5.05	5.01	4.81
SD	0.03	0.03	0.02	0.01	0.01	0.04	0.06
95 % CONFIDENCE INTERVAL	0.03	0.04	0.03	0.01	0.02	0.05	0.07
PERCENTAGE OF ORIGINAL CONCENTRATION (%)	100	96.4	95.4	96.2	96.4	95.6	91.8

Table 3. Stability of 10 mg/mL Omeprazole Oral Mix Dry Alka, SF (Cherry Flavored) stored in 100 mL amber PP UV-resistant (low actinic) bottles at 4 °C

PARAMETER	DAY						
	0	7	14	28	42	56	70
APPEARANCE	Opaque suspension - normal appearance	✓	✓	✓	✓	✓	✓
COLOR	Off-white	✓	✓	✓	✓	✓	✓
ODOR	Odorless	✓	✓	✓	✓	✓	✓
RESUSPENDABILITY	Easily resuspended – no evidence of caking	✓	✓	✓	✓	✓	✓
pH (7-9)	9.03	8.76	8.74	8.75	8.27	8.03	7.84
ASSAY (mg/mL)	10.62	10.22	10.05	10.08	10.22	10.18	9.65
SD	0.19	0.22	0.23	0.14	0.18	0.04	0.26
95 % CONFIDENCE INTERVAL	0.21	0.25	0.26	0.16	0.20	0.05	0.29
PERCENTAGE OF ORIGINAL CONCENTRATION (%)	100	96.2	94.6	94.9	96.2	95.9	90.9

✓= Conforms to Specification

Conclusion

All omeprazole suspensions studied 2, 5 and 10 mg/mL, stored in amber, PP UV-Resistant (low actinic) bottles at 4 °C were physically and chemically stable for up to 70 days. Based on these bracketed study results and the FDA's guidance on bracketed study design, any concentration of omeprazole suspension at or between 2 to 10 mg/mL in Oral Mix Dry Alka, SF (Cherry Flavored) stored in amber, PP UV-Resistant (low actinic) bottles at 4 °C can be considered stable for a 70-day extended beyond-use-date. This demonstrates that Oral Mix Dry Alka, SF (Cherry Flavored) is a suitable suspending vehicle for compounding omeprazole in a wide range of concentrations, especially for situations where capsules are not appropriate therapeutic options.

References

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