Stability of Extemporaneously Prepared Enalapril Maleate Suspensions in Glass Bottles and Plastic Syringes

Enalapril maleate is available in Canada as tablets (2.5, 5, 10, and 20 mg) but not as oral suspensions. It is used to treat hypertension[1,2] and congestive heart failure[3,4] in both adult and pediatric patients. Nahata and others[5] reported that enalapril maleate suspensions (1 mg/mL) in citrate buffer and in a 1:1 mixture of Ora-Plus and Ora-Sweet vehicles were stable for at least 91 days (at 4°C or 25°C); in water, the period of stability was reduced to 56 days (at 25°C).

Commercially available vehicles facilitate the preparation of compounded preparations. Currently, the stability of enalapril maleate is known for only one commercially available vehicle (Ora-Blend [a 1:1 mixture of Ora-Plus and Ora-Sweet]); the supply chain for enalapril maleate suspensions is therefore vulnerable to back orders or other unfortunate situations. Also, some patients are allergic to or intolerant of the ingredients in some vehicles; having an alternative vehicle is therefore advisable. This study was undertaken to investigate the stability of enalapril maleate suspensions (1 mg/mL) prepared in Oral Mix, a dye-free acidic suspending vehicle.

Enalapril maleate suspensions (1 mg/mL) were prepared by wetting bulk powder (230 mg; Medisca Pharmaceutique Inc, Montréal, Quebec; lot 48336/B, expiry October 2015) with polysorbate 80 (250 µL; Sigma Aldrich, Oakville, Ontario; lot MKBJ0197V) and Oral Mix vehicle (500 µL; Medisca Pharmaceutique Inc; lot I074/A, expiry February 2015). Oral Mix was geometrically added to the resulting paste to bring to a final volume of 230 mL. Similar suspensions were prepared from enalapril maleate tablets crushed in a mortar (12 × 20-mg Vasotec tablets; Merck Canada, Kirkland, Quebec; lot HO21040, expiry February 2014) and completed with geometric addition of Oral Mix to a final volume of 240 mL.

The suspensions were packaged in bottles (6 × 30-mL samples; amber glass Wheaton type 1, 50-mL bottles, Medisca Pharmaceutique Inc, lot 24908/A) and plastic syringes (48 × 1-mL samples; PreciseDose Dispenser, 1-mL volume, Medisca Pharmaceutique Inc, lot 55052/A, with tip cap, lot 46968/C) and stored at 5 ± 2°C (ambient relative humidity) or 25 ± 2°C (relative humidity 60% ± 5%), for up to 90 days (Forma 3911 environmental chamber, Thermo Scientific, Rochester, New York).

At predetermined intervals, all samples were examined for changes in colour and odour, the pH was measured (pH meter 211, Hanna Instruments, Montréal, Quebec), and quantification by high-performance liquid chromatography with ultraviolet detection (HPLC-UV) was performed.

The HPLC-UV method used a mobile phase consisting of acetonitrile–methanol–monopotassium phosphate buffer 10 mmol/L (10:30:60), with pH adjusted to 2.5 using phosphoric acid (acetonitrile and methanol [both of HPLC grade], Fisher Scientific, Ottawa, Ontario; monopotassium phosphate, J T Baker, Phillipsburg, New Jersey; phosphoric acid 8.5%, LabMAT, Montréal, Quebec; purified water, Milli-Q Synthesis A10, Millipore, Etobicoke, Ontario).

Samples for HPLC injection were prepared by diluting the suspension (50 µL) with phosphate buffer and methanol (950 µL of a 1:1 mixture), vigorously mixing (10 s; Vortex Genie 2 mixer, Scientific Industries Inc, Bohemia, New York) and then centrifuging (10 000 rpm for 15 min; Centrifuge 5424, Eppendorf, Mississauga, Ontario). The supernatant was transferred into a sealed 96-well plate (0.5-mL, PK20, VWR International, Ville Mont-Royal, Quebec) and analyzed by HPLC-UV (Prominence UFLC system, Shimadzu, Laval, Quebec): flow rate 1 mL/min; autosampler set at 10°C; C18 4.6 × 150 mm, 3.5-µm column (Zorbax Eclipse, Agilent Technologies, Montréal, Quebec) at 60°C; and UV wavelength 210 nm.

Recovery of the sample preparation was 101.1% (suspensions in Oral Mix submitted to sample preparation [n = 6] relative to drug in methanol, 50 µg/mL [n = 3]).

For calibration of the HPLC-UV method, 5 standard solutions (0, 25, 50, 75, and 100 µg/mL) were prepared from a stock solution in methanol (1 mg/mL) and phosphate buffer (r^2 = 0.9999, n = 3).

At target concentration, the intraday variability was 2.0% and 0.6% for preparations made from bulk powder and tablets, respectively (n = 6). The interday variability was 0.5% and 0.8% for preparations made from bulk powder and tablets, respectively (3 days, n = 6). The interday variability was 0.4% for enalapril maleate solutions in methanol (50 µg/mL, 3 days, n = 3).

Forced degradation experiments, which involved enalapril maleate suspensions 1 mg/mL in Oral Mix, diluted 2-fold in each diluent, with heating at 60°C for 2 h, resulted in the following recoveries: 103.4% for drug in purified water, 54.3% in alkaline conditions (sodium hydroxide 0.1N), 99.1% in acidic conditions (hydrochloric acid 0.1N), and 94.3% in oxidative conditions (hydrogen peroxide 3%).

No overlap was observed between the enalapril peak and peaks of degradation products in any of forced degradation experiments,

Table 1. Chemical Stability of Enalapril Maleate Suspension Prepared from Bulk Powder

	Mean Concentration ± SD (mg/mL) and Mean % Remaining*			
Study Day	**Packaged in Amber Glass Bottles**		**Packaged in Amber Plastic Syringes**	
Storage at 5°C, ambient RH				
Initial	1.009 ± 0.020	(100.0)	1.009 ± 0.020	(100.0)
7	0.992 ± 0.004	(98.3)	1.008 ± 0.009	(99.8)
14	1.003 ± 0.010	(99.4)	1.007 ± 0.015	(99.7)
30	0.969 ± 0.005	(96.0)	0.939 ± 0.008	(93.0)
45	0.971 ± 0.001	(96.2)	0.965 ± 0.003	(95.6)
60	1.003 ± 0.023	(99.3)	0.999 ± 0.011	(99.0)
75	1.018 ± 0.003	(100.8)	1.026 ± 0.002	(101.7)
90	1.014 ± 0.002	(100.5)	1.018 ± 0.007	(100.9)
Storage at 25°C, 60% RH				
Initial	1.009 ± 0.020	(100.0)	1.009 ± 0.020	(100.0)
7	1.011 ± 0.028	(100.1)	0.997 ± 0.013	(98.8)
14	0.997 ± 0.004	(98.8)	1.003 ± 0.011	(99.3)
30	0.935 ± 0.001	(92.6)	0.992 ± 0.005	(98.3)
45	0.996 ± 0.003	(98.7)	0.997 ± 0.005	(98.8)
60	0.945 ± 0.012	(93.6)	0.937 ± 0.010	(92.9)
75	0.970 ± 0.003	(96.1)	0.966 ± 0.001	(95.7)
90	0.954 ± 0.013	(94.5)	0.963 ± 0.008	(95.4)

RH = relative humidity, SD = standard deviation.
*Mean concentrations are based on 3 separate samples; the percentage remaining is relative to the initial measured concentration.

Table 2. Chemical Stability of Enalapril Maleate Suspension Prepared from Tablets

	Mean Concentration ± SD (mg/mL) and Mean % Remaining*			
Study Day	**Packaged in Amber Glass Bottles**		**Packaged in Amber Plastic Syringes**	
Storage at 5°C, ambient RH				
Initial	1.038 ± 0.006	(100.0)	1.038 ± 0.006	(100.0)
7	1.051 ± 0.002	(101.2)	1.038 ± 0.003	(100.0)
14	1.029 ± 0.005	(99.1)	1.026 ± 0.003	(98.8)
30	1.019 ± 0.005	(98.1)	1.018 ± 0.007	(98.0)
45	1.003 ± 0.012	(96.7)	0.997 ± 0.003	(96.1)
60	1.025 ± 0.008	(98.7)	1.025 ± 0.009	(98.8)
75	1.042 ± 0.002	(100.3)	1.037 ± 0.005	(99.9)
90	1.033 ± 0.007	(99.5)	1.032 ± 0.001	(99.4)
Storage at 25°C, 60% RH				
Initial	1.038 ± 0.006	(100.0)	1.038 ± 0.006	(100.0)
7	1.033 ± 0.013	(99.5)	1.023 ± 0.003	(98.5)
14	1.015 ± 0.022	(97.8)	1.017 ± 0.025	(98.0)
30	0.994 ± 0.022	(95.7)	0.978 ± 0.012	(94.2)
45	0.990 ± 0.004	(95.4)	0.986 ± 0.005	(95.0)
60	0.977 ± 0.034	(94.1)	0.963 ± 0.005	(92.8)
75	0.950 ± 0.004	(91.5)	0.959 ± 0.018	(92.4)
90	0.946 ± 0.018	(91.1)	0.943 ± 0.007	(90.8)

RH = relative humidity, SD = standard deviation.
*Mean concentrations are based on 3 separate samples; the percentage remaining is relative to the initial measured concentration.

with similarity indexes between 190 and 240 nm of not less then 0.9999. All non-enalapril peaks eluted between 1 and 5 min, whereas enalapril eluted at 5.7 min.

Throughout the study, the pH varied between 4.2 and 4.3 for preparations made from bulk powder and between 4.5 and 4.6 for those made from tablets. All suspensions were easily resuspended, with no changes in colour or odour.

The HPLC-UV results relative to measured concentration at time zero are presented in Tables 1 and 2. The average recovery was not less than 90.0% in all cases.

Enalapril maleate suspensions in Oral Mix (1 mg/mL) were stable for at least 90 days under all conditions studied here: prepared from bulk powder or tablets, stored in glass bottles or syringes, and stored at 5°C or 25°C. These results are similar to the findings of

previous studies involving other acidic vehicles.[5,6] The Vasotec 20-mg tablets used in this study represent an immediate-release formulation containing, in addition to the drug, corn starch, lactose, magnesium stearate, pregelatinized starch, and sodium bicarbonate. This product was used only as a reference; generic brands of enalapril maleate tablets could also be used, so long as they are bioequivalent to this reference product.

Given the results of this study, Oral Mix is a safe dye-free alternative to other vehicles for the compounding of enalapril maleate suspensions.

References

1. Meyers RS, Siu A. Pharmacotherapy review of chronic pediatric hypertension. *Clin Ther.* 2011;33(10):1331-56.
2. Robinson RF, Nahata MC, Batisky DL, Mahan JD. Pharmacologic treatment of chronic pediatric hypertension. *Pediatr Drugs*. 2005;7(1):27-40.
3. Moffett BS, Price JF. National prescribing trends for heart failure medications in children. *Congenit Heart Dis.* 2015;10(1):78-85.
4. Momma K. ACE inhibitors in pediatric patients with heart failure. *Pediatr Drugs.* 2006;8(1):55-69.
5. Nahata MC, Morosco RS, Hipple TF. Stability of enalapril maleate in three extemporaneously prepared oral liquids. *Am J Health Syst Pharm.* 1998;55(11): 1155-7.
6. Casas M, Alvarez J, Lucero MJ. Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients. *Pharm Dev Technol.* 2015;20(3):271-8.

Mihaela Friciu, MSc
Research Associate
Sarra Zaraa, MSc
Research Associate
Grégoire Leclair, BPharm, PhD
Associate Professor
Faculty of Pharmacy
Université de Montréal
Montréal, Quebec

Competing interests: None declared.

Funding: This study was funded by an unrestricted grant from Medisca Pharmaceutique Inc, Montréal, Quebec. The company was not involved in the design or conduct of the study; the collection, management, or interpretation of the data; or the preparation, review, or approval of the manuscript.