Stability of dolasetron in two oral liquid vehicles

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D olasetron mesylate is an antinauseant and antiemetic agent. It is a highly specific, selective inhibitor of type 3-serotonin receptors (5-HT₃) both in vitro and in vivo.^{1,2} Dolasetron belongs to a class of medications known as 5-HT₃ antagonists, which are considered to be the most potent antiemetic compounds available today. A pseudopelletierine derivative, dolasetron retains the indole nucleus of serotonin and bears structural similarity to ondansetron and tropisetron.³

Dolasetron is used i.v. or orally for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy and also is used i.v. or orally for the prevention of postoperative nausea and vomiting and i.v. for the treatment of postoperative nausea and vomiting.² The recommended i.v. and oral dosage for the prevention of chemotherapy-induced nausea and vomiting is 1.8 mg/kg for patients 2 years of age or older to a maximum of 100 mg.^{1,3} The recommended dosage for the treatment or prevention of postoperative nausea and vomiting is 0.35 mg/kg i.v. for patients 2-16 years old with a maximum dose of 12.5 mg. The recommended oral dosage for the prevention of postoperative nausea and **Abstract:** The stability of dolasetron 10 mg/mL over 90 days when prepared as an oral liquid formulation from commercially available tablets in both strawberry syrup and a sugar-free vehicle was studied.

A liquid suspension of dolasetron mesylate 10 mg/mL was prepared from commercially available dolasetron tablets, Ora-Plus, and Ora-Sweet or strawberry syrup. Six samples of each formulation were prepared and stored in amber plastic bottles. Three samples of each formulation were refrigerated (3-5 °C) and three were stored at room temperature (23-25 °C). A 1-mL sample was withdrawn from each of the 12 bottles immediately and after 7, 14, 30, 60, and 90 days. After further dilution to an expected concentration of 10 µg/mL with sample diluent, the solutions were assayed in duplicate using high-performance liquid chromatography. The samples were also inspected for color and odor changes, and the pH of each sample was determined. The stability-

vomiting is 1.2 mg/kg in patients 2– 16 years old, given within two hours before surgery, up to a maximum of 100 mg.^{1,3} Dolasetron's safety and effectiveness in patients under age 2 have not been established.¹

Dolasetron mesylate is available in the United States as 50- and 100-mg oral coated tablets and as a 20-mg/ mL injection. An oral liquid dosage formulation is not commercially available. A liquid formulation indicating capability of the dolasetron assay was determined by forced degradation of four separate 10-mg/mL samples exposed to direct sunlight for 90 days.

There were no detectable changes in color, odor, or taste and no visible microbial growth in any sample. At least 98% of the initial dolasetron concentration remained throughout the 90-day study period for all samples.

An extemporaneously compounded oral liquid preparation of dolasetron mesylate 10 mg/mL in a 1:1 mixture of Ora-Plus and strawberry syrup or Ora-Sweet was stable for at least 90 days when stored at 3–5 or 23–25 °C.

Index terms: Antiemetics; Color; Concentration; Contamination; Dolasetron; Hydrogen ion concentration; Odors; Photodecomposition; Stability; Storage; Suspensions; Taste; Temperature; Vehicles

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would be advantageous for both pediatric and adult patients who are unable to swallow tablets or who must receive medications by nasogastric or gastrostomy tubes. Such a formulation would also be advantageous for patients requiring nonstandard dosages of dolasetron that would be more easily and accurately measured using a liquid formulation. According to the manufacturer, the injection form may be mixed in ap-

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ple or apple-grape juice for oral administration in pediatric patients, and the diluted product may be kept for up to two hours at room temperature before use.1 The recommended dosage of diluted injection used orally in patients 2-16 years old is 1.2 mg/kg for prevention of postoperative nausea and vomiting, and 1.8 mg/kg for prevention of cancer chemotherapy nausea and vomiting, up to a maximum of 100 mg.¹To date, no studies have evaluated the stability of an oral liquid preparation of dolasetron. The availability of extendedstability information for dolasetron oral liquid will allow hospitals, health care centers, and ambulatory care pharmacies to compound oral liquid dosage forms to better meet the needs of individual patients. In addition, using a sugar-free preparation as a vehicle would benefit patients on a ketogenic, diabetic, or oral liquid diet or those with other dietary restrictions. Extemporaneously compounded drug formulations are important in the treatment of pediatric patients.⁴ These patients require dosages based on body weight, as fixed doses in tablets and capsules intended for adults cannot be given to infants and children.⁵

The purposes of this study were to prepare an oral liquid dosage form of dolasetron mesylate from commercially available 50-mg tablets in both strawberry syrup and a sugar-free vehicle and determine the short-term physical and chemical stability of these preparations over 90 days.

Methods

Sample preparation. A liquid suspension of dolasetron mesylate 10 mg/mL was prepared by thoroughly crushing 12 tablets of dolasetron mesylate 50 mg^a in a glass mortar. Ora-Plus^b and strawberry syrup or Ora-Plus and Ora-Sweet SF^c were combined in a 1:1 ratio and slowly added to the crushed dolasetron to make a final volume of 60 mL. The strawberry syrup was prepared by

mixing 3200 mL of simple syrup, NF,^d and 600 mL of strawberry fountain syrup.^e Details of the procedure are given in the appendix.

Six identical samples of each formulation (Ora-Plus and strawberry syrup, Ora-Plus and Ora-Sweet SF) were prepared and placed in 2-oz amber plastic bottles with childresistant caps.^f Three samples of each formulation were refrigerated (3-5 °C) and three samples were stored at room temperature (23-25 °C). A 1mL sample was withdrawn from each of the 12 bottles with a micropipette immediately after preparation and at 7, 14, 30, 60, and 90 days. After further dilution to an expected concentration of 10 μ g/mL with sample diluent (acetonitrile and deionized filtered water, 24:76, by volume), the solutions were assayed in duplicate using high-performance liquid chromatography (HPLC).6,7

Each of the dolasetron samples was shaken thoroughly by hand for approximately 15 seconds immediately before assay. All samples were centrifuged at 1000 rpm for two minutes to separate the insoluble components. Five microliters of each sample was injected into the HPLC system, and each sample was assayed in duplicate.

HPLC assay. The HPLC method developed by Gillespie et al.⁸ was modified for use in this study. The instrumentation included a constant-flow solvent delivery system,^g a C_{18} column^h maintained at 30 °C with a column heater,ⁱ a variable volume injector,^j an ultraviolet light detector^k set at 280 nm, and a recording integrator.¹ The mobile phase consisted of acetonitrile and aqueous 0.05 M ammonium acetate adjusted to a pH of 7.5 with dilute ammonium hydroxide (24:76, by volume), delivered at a flow rate of 0.8 mL/min.

The stability-indicating capability of the dolasetron assay was determined in our laboratory. Degradation of dolasetron was forced by exposing four separate 10-mg/mL samples (two in syrup and two in a sugar-free vehicle) to direct sunlight for 90 days after adjusting the pH to 12 with 1 N sodium hydroxide (one sample of each vehicle) or to a pH of 2 with 1 N hydrochloric acid (one sample of each vehicle). The solutions were then heated to 60 °C for two hours. The pH was adjusted to 7, and the solutions were diluted with sample diluent to an expected concentration of 10 µg/mL and assayed. Approximately 98% degradation was achieved with the basic solution, and essentially no degradation occurred using the acidic solution; no interfering peaks were found after assay at three different wavelengths. The peak for dolasetron appeared at 6.9 minutes.

Preparation of standard solutions and standard curve. A 500-µg/ mL stock solution of analytic-grade dolasetron mesylate^m was prepared in sample diluent on each day of HPLC analysis. Standard solutions of dolasetron were prepared by diluting the stock solution with mobile phase to concentrations of 8, 9, 10, 11, and 12 µg/mL. A 10-µg/mL concentration of dolasetron was assayed in duplicate after approximately every 10th sample as an external control. A standard curve was produced on each day of sample analysis using linear regression of the peak heights of dolasetron against dolasetron mesylate concentration. The standard curve was linear ($r^2 > 0.999$) over the working range of concentrations. The between-day and within-day coefficients of variation for the dolasetron assay were 2.65% and 1.31%, respectively. In addition, each sample was visually inspected for any color change, evaluated for odor, pH tested,ⁿ and taste tested on each day of analysis. Microbiological testing was not performed because each vehicle contained effective preservatives.

Data analysis. The stability of dolasetron was determined by evaluating the percentage of the initial concentration remaining at each time Table 1

Suspension ^a	Storage Temperature (°C)	Actual Initial Drug Concentration ^b (mg/ml)	% Initial Concentration Remaining ^b				
			Day 7	Day 14	Day 30	Day 60	Day 90
А	3–5 23–25	9.94 ± 0.08 9.94 ± 0.08	99.34 ± 1.34 100.61 + 1.23	100.00 ± 1.51 100.40 ± 1.64	99.87 ± 1.68 99.83 + 0.40	99.57 ± 1.28 99.82 + 0.84	99.34 ± 1.31 99.54 ± 0.89
В	3–5 23–25	9.91 ± 0.05 9.91 ± 0.05	99.61 ± 1.19 99.41 ± 1.05	$\begin{array}{c} 99.83 \pm 1.40 \\ 98.75 \pm 1.40 \end{array}$	$99.58 \pm 1.40 \\ 100.17 \pm 1.15$	$\begin{array}{c} 100.01 \pm 1.11 \\ 99.82 \pm 1.39 \end{array}$	99.08 ± 1.39 100.46 ± 1.18

Stability of Dolasetron Mesylate 10 mg/mL in Two Vehicles at 3-5 and 23-25 °C

^aA = dolasetron tablets, Ora-Plus, and strawberry syrup; B = dolasetron tablets, Ora-Plus, and Ora-Sweet SF.

^bMean \pm S.D. of duplicate determinations for three samples (n = 3).

interval. Stability of the dolasetron oral liquid formulation was defined as the retention of at least 90% of the initial concentration.

Results and discussion

At least 98% of the initial concentration of dolasetron mesylate remained throughout the 90-day study period in all suspensions (Table 1). There were no detectable changes in color, odor, or taste and no visible microbial growth in any sample. No appreciable change from the initial mean \pm S.D. pH (4.10 \pm 0.01) existed in any of the samples containing strawberry syrup or in those prepared with Ora-Sweet SF (4.03 \pm 0.03). Both preparations were sweet with a slightly bitter aftertaste, with no appreciable change over time. Taking chocolate syrup before medication administration and mixing the suspension with chocolate syrup (1:1) are recommended to mask the bitter aftertaste and improve palatability, especially for children.

The absorption of dolasetron mesylate has been reported to be approximately 75%, determined by its major active metabolite, hydrodolasetron.¹ The absorption of the dolasetron mesylate formulation used in this study has not been evaluated. However, the absorption and therapeutic effectiveness of a drug in a suspension compounded from crushed tablets are unlikely to differ appreciably from those of the original dosage form.

Conclusion

An extemporaneously compounded oral liquid preparation of dolasetron mesylate 10 mg/mL in a 1:1 mixture of Ora-Plus and strawberry syrup or Ora-Sweet SF was stable for at least 90 days when stored at 3–5 or 23–25 °C.

- [°]Ora-Sweet SF, Paddock, lot 1474447.
- ^dSimple syrup, NF, Humco Laboratory, Texarkana, TX, lot 148610.

^eStrawberry fountain syrup, Gordon Food Service, Grand Rapids, MI, lot K553909117.

¹2-oz amber prescription bottles with childresistant caps, Owens Illinois Prescription Products, Owens Illinois, OH.

^gHPLC pump, Waters Associates, Inc., Milford, MA, model 501.

 $^{\rm h}{\rm Spherisorb}$ CN, 3-µm particle size, 150 \times 4.6 mm, P. J. Cobert Associates, Inc., St. Louis, MO.

ⁱEppendorf CH-30 column heater, P. J. Cobert.

^JVariable-volume injector, Waters, model U6K.

^kTunable absorbance detector, model 486, Waters.

¹Integrator-recorder, Hewlett Packard, model 3394, Avondale, PA.

^mDolasetron mesylate analytic-grade powder, Aventis Pharmaceuticals, lot MDL073147EF-089.

ⁿAltex pH 41 meter, Beckman Instruments, Irvine, CA.

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Appendix—Procedure for compounding dolasetron 10-mg/mL oral liquid

- 1. Count out 12 50-mg Anzemet tablets.
- 2. Pulverize the 12 tablets in a glass mortar to produce a fine powder.
- 3. Mix 30 mL of Ora-Plus with 30 mL of strawberry syrup or Ora-Sweet SF; stir vigorously.
- 4. Add approximately 15 mL of the desired mixture to the powder, triturate well, and transfer the contents to a 2-oz child-resistant amber plastic prescription bottle.
- 5. Rinse the mortar with about 15 mL of the mixture and transfer the contents to the amber prescription bottle.
- 6. Repeat step 5 as necessary with enough syrup mixture to bring the final volume to 60 mL.
- 7. Label the bottle "Shake Well Before Use."

^aDolasetron mesylate 50-mg tablets, Aventis Pharmaceuticals, Inc., Kansas City, MO, lot 3025410.

^bOra-Plus, Paddock Laboratories, Minneapolis, MN, lot 2296122.

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