VOLUME 17 NUMBER 1

Secundum Artem

Current & Practical Compounding Information for the Pharmacist

An ongoing CE Program provided by a grant from Perrigo Pharmaceuticals.

Stability of Extemporaneously Prepared Oral Liquid Formulations – Part IX

GOALS AND OBJECTIVES

Goal: To provide information from the peer-reviewed literature on stability studies of oral liquids.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss the factors involved in using commercial products as the source of drug for compounding.
2. Describe which dosage forms should not be used in compounding, unless their suitability has been confirmed.
3. Evaluate the data presented to determine a beyond-use date for the compounded oral liquids.
4. Generally describe the compounding procedures used in extemporaneously compounding oral liquids.

INTRODUCTION

The preparation of oral liquid formulations generally uses either bulk powders or commercial products. Ideally, bulk powders are used as one knows their purity/strength from the accompanying Certificate of Analysis. However, commercial products must sometimes be used. Considerations concerning commercial product use include the following:

1. All the excipients present in the commercial dosage form must be considered for their effects on the efficacy, safety, stability and assay potency of the final compounded preparation.
2. When using solutions as the source of drugs, the pH of the solution and the desired pH of the final compounded preparation should be considered. If there is a significant difference in pH (i.e., 2 to 3 pH units), the solubility and stability of the drug and formulation may change.
3. The presence of buffers in the commercial drug product can affect the pH of the final compounded preparation.
4. If preparing large batches, it may be advisable to assay the commercial product for potency and make any necessary adjustments.
5. Modified-release dosage forms (e.g., extended release, delayed release, repeat action, targeted release) should not be used unless their suitability for use in compounding has been documented.
6. If available from multiple sources, use the same manufacturer if possible.
7. Occassionally, the required quantity makes use of the commercial product impractical.

The extemporaneous preparations presented in this paper, many of which use commercial products, include those listed in Table 1.

Table 1: Concentrations of the various drugs in the studies reported in this paper.

Drug	Concentration (mg/mL)
Clonidine hydrochloride	0.1 mg/mL
Glycopyrrolate	0.5 mg/mL
Levothyroxine sodium	25 µg/mL
Melatonin	1 mg/mL
Oseltamivir phosphate	6 mg/mL
Tadalafil	5 mg/mL
Thioguanine	20 mg/mL
Vancomycin	25 mg/mL
Ziprasidone mesylate	2.5 mg/mL
Zonisamide	10 mg/mL

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Clonidine Hydrochloride 0.1 mg/mL Oral Suspension

Clonidine hydrochloride ($C_9H_9Cl_2N_3$ •HCl, MW 266.56, Catapres®) occurs as a white to almost white crystalline powder with a bitter taste. It is soluble about 77 mg/mL in water and is soluble in alcohol. It should be protected from light. Each tablet for oral administration also contains colloidal silicon dioxide, corn starch, dibasic calcium phosphate, FD&C Yellow No. 6, gelatin, glycerin, lactose, magnesium stearate, methylparaben and propylparaben (1991 PDR).

The preparation was compounded by grinding commercially available 0.2 mg clonidine hydrochloride tablets, adding Purified Water USP to form a paste, and adding Simple Syrup NF to volume resulting in a 0.1 mg/mL preparation. A duplicate preparation (solution) was made using clonidine hydrochloride powder. Samples were stored in amber glass prescription bottles and stored at refrigerated temperatures. Samples were obtained periodically for up to 28 days. After 28 days, the remaining clonidine hydrochloride was at 92.4% in the suspension and 93.7% in the solution. The color, odor and pH did not change appreciably over the study period. Both preparations were stable for the 28 day study period.[1]

Table 2: Stability of two formulations of clonidine hydrochloride 0.1 mg/mL in Simple Syrup NF stored at 4° C.

Formulation	% of Initial Concentration Remaining				
	Day 3	Day 7	Day 14	Day 21	Day 28
Solution	97.2 (0.6)	97.4 (0.4)	101.0 (1.5)	101.2 (0.9)	93.7 (1.3)
Suspension	99.6 (3.0)	101.1 (2.2)	98.9 (1.3)	98.6 (4.4)	92.4 (1.6)

Glycopyrrolate 0.5 mg/mL Oral Suspension

Glycopyrrolate ($C_{19}H_{28}BrNO_3$, MW 398.33, Robinul®) occurs as a white, odorless, crystalline powder that is soluble in water and in alcohol. It is soluble in water (about 238 mg/mL) and in alcohol (about 33 mg/mL). Glycopyrrolate stability is pH-dependent in aqueous solution; being very stable up to a pH of 5.[2] Each 1 mg tablet contains the inactive ingredients: dibasic calcium phosphate, lactose, magnesium stearate, povidone and sodium starch glycolate.

Glycopyrolate 0.5 mg/mL oral suspension was prepared by grinding glycopyrrolate 1 mg tablets in a glass mortar. Ora-Plus® with either Ora-Sweet® or Ora-Sweet® SF were mixed and added to the powder to final volume. The preparation was placed in amber plastic bottles and stored at 23-25° C. There were no detectable changes in color, odor, taste, and pH and no visible microbial growth was observed in any sample. The compounded suspensions were stable for at least 90 days when stored in amber plastic bottles at room temperature.

Table 3: Stability of glycopyrrolate 0.5 mg/mL in Ora-Plus with either Ora-Sweet or Ora-Sweet SF in plastic bottles at room temperature.[3]

Formulation	% of Initial Concentration Remaining				
	Day 7	Day 15	Day 30	Day 60	Day 90
Ora-Plus: Ora-Sweet	99.02 (1.72)	99.12 (0.12)	95.53 (2.62)	100.12(1.53)	98.63 (1.38)
Ora-Plus: Ora-Sweet SF	98.74 (0.71)	99.36 (0.87)	97.28 (0.66)	100.26 (1.40)	99.19 (1.63)

Levothyroxine Sodium 25 µg/mL Oral Suspension

Levothyroxine sodium ($C_{15}H_{10}I_4N\ NaO_4$ •H_2O, MW 798.86 (anhydrous), Levothroid®, Levoxyl®, Synthroid®) occurs as a light yellow to buff-colored, odorless, tasteless, hygroscopic powder. It is stable in dry air but may become a slight pink color upon exposure to light. The pH of a saturated solution is about 8.9. It is slightly soluble in alcohol and very slightly soluble in water.[2] Levothyroxine tablets (Synthroid) also contain acacia, confectioner's sugar, lactose monohydrate, magnesium stearate, povidone, and talc, along with various dyes, depending upon tablet strength.

Levothyroxine sodium oral liquid 25 µg/mL was prepared with and without methylparaben preservative (0.1%). Levothyroxine sodium tablets were ground to a fine powder with a ceramic mortar and pestle. Forty mL of glycerin was measured and a small portion of glycerin was mixed with the powder. The mixture was then transferred to a calibrated 100 mL amber, high-density polyethylene bottle. The mortar was rinsed with about 10 mL of glycerin and this process repeated until the glycerin is used. Purified water (preserved or nonpreserved) was added to volume and mixed well. Samples were stored at 2-8°C and 23-27° C. Samples were obtained initially and after 3, 8, 14, 22, 31, 61 and 90 days. Results showed that an extemporaneous oral liquid formulation of levothyroxine sodium 25 µg/mL in 40% glycerin compounded from crushed tablets was stable for 8 days when stored in amber high-density polyethylene bottles at 4° C.[4]

Table 4: Stability of two formulations of levothyroxine sodium 25 µg/mL in water stored at 2-8°C and 23-27° C.

Formulation		% of Initial Concentration Remaining			
		Day 8	Day 14	Day 31	Day 90
Unpreserved	4° C	94.4 (2.5)	90.0 (1.9)	81.7 (3.5)	68.2 (4.8)
	25° C	94.7 (2.3)	88.0 (4.5)	72.4 (3.6)	58.0 (3.5)
Preserved	4° C	91.5 (3.6)	85.1 (5.1)	77.8 (3.0)	64.3 (4.1)
	25° C	91.4 (1.7)	83.5 (2.4)	65.9 (2.4)	57.0 (3.4)

Melatonin 1 mg/mL Oral Suspension

Melatonin ($C_{13}H_{16}N_2O_2$, MW 232.3; 5-methoxy-N-acetyltryptamine) is currently marketed as a dietary supplement. Products that are commercially available include tablets, extended-release capsules and tablets, sublingual tablets, intraoral sprays and oral liquids. However, the oral liquid preparations contain alcohol and are not recommended in the pediatric population.

Melatonin 1 mg/mL oral suspension was prepared by crushing the tablets and combined with a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF. The suspensions were placed in amber plastic prescription bottles and stored at room temperature. Samples were removed at 7, 15, 30, 60 and 90 days. Results showed these preparations to be stable for at least 90 days.[5]

Table 5: Stability of melatonin 1 mg/mL in Ora-Plus with either Ora-Sweet or Ora-Sweet SF in plastic bottles at room temperature.

Formulation	% of Initial Concentration Remaining				
	Day 7	Day 15	Day 30	Day 60	Day 90
Ora-Plus: Ora-Sweet	99.38 (0.69)	99.11 (0.58)	99.59 (0.82)	98.19 (1.44)	94.93 (1.60)
Ora-Plus: Ora-Sweet SF	99.96 (0.62)	100.62 (0.33)	99.91 (0.54)	101.55 (2.06)	101.01 (0.26)

*pH for Ora-Plus; Ora-Sweet mixtures was 4.80 (0.04) and for Ora-Plus; Ora-Sweet SF mixtures was 4.87 (0.02)

Oseltamivir Phosphate 6 mg/mL Oral Suspension

Oseltamivir phosphate ($C_{16}H_{28}N_2O_4 \bullet H_3PO_4$, MW 410.40, Tamiflu®) occurs as a white to off-white powder. It is freely soluble in water (about 588 mg/mL) and soluble in propylene glycol. It is slightly soluble in alcohol. It should be protected from light.[2] Oseltamivir phosphate (Tamiflu) capsules also contain pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate. The gelatin shells also contain gelatin and coloring agents.

The preparation was compounded by placing about 7 mL of purified water in a polyethylene terephthalate plastic or glass bottle. The contents of eight Tamiflu 75 mg capsules are placed in the container followed by swirling for at least 2 minutes to ensure wetting of the powder. Sufficient Ora-Sweet SF or Cherry Syrup (Humco®) or simple syrup are added to volume and shaken well for 30 seconds resulting in a suspension. The preparation is stable for 35 days when stored at 2-8° C or for 5 days when stored at 25° C.[6] This compounding information is included in the Tamiflu Package Insert under Section 2.8 Emergency Compounding of an Oral Suspension from 75 mg TAMIFLU Capsules (Final Concentration 6 mg/mL).

Tadalafil 5 mg/mL Oral Suspension

Tadalafil ($C_{22}H_{19}N_3\ O_4$, MW 389.40, Cialis®) It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol. Each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

The suspension was compounded by grinding tadalafil tablets in a glass mortar. Ora-Plus and Ora-Sweet were mixed 1:1 and added to the powder to final volume. The suspension was placed in amber plastic bottles and stored at 23-25° C. Samples were obtained immediately and after 7, 14, 28, 57 and 91 days. The samples were evaluated for pH and color change and taste evaluation was performed at the beginning and end of the study.

The results showed that at least 99% of the initial tadalafil concentration remained throughout the 91 day study period and there were no detectable changes in color, odor, taste and pH and no visible microbial growth.[7]

Thioguanine 20 mg/mL Oral Suspension

Thioguanine ($C_5H_5N_5S \bullet H_2O$, MW 167.19 (anhydrous)) occurs as a pale yellow, odorless or practically odorless, crystalline powder. It is insoluble in water and in alcohol.[2] The TABLOID® brand thioguanine tablets contains 40 mg thioguanine and the inactive ingredients acacia, lactose monohydrate, magnesium stearate, potato starch, and stearic acid.

Thioguanine 20 mg/mL oral suspension was prepared by triturating thioguanine tablets and mixing them with 33% Ora-Plus and sufficient Ora-Sweet to volume. The suspension was packaged in amber glass bottles and stored at 19-23° C. They were evaluated for appearance, pH and content weekly. The results show that thioguanine 20 mg/mL suspension in Ora-Plus and Ora-Sweet was chemically and physically stable for up to nine weeks at 19-23° C.[8]

Vancomycin 25 mg/mL Oral Suspension

Vancomycin hydrochloride ($C_{66}H_{75}Cl_2N_9O_{24} \bullet HCl$, MW 1485.71, Vancocin®) occurs as a white, almost white, or tan to brown, free-flowing odorless powder with a bitter taste. It is freely soluble in water. Vancomycin Hydrochloride for Injection USP is a sterile dry mixture of vancomycin hydrochloride and may contain a suitable stabilizing agent.[2]

Vancomycin hydrochloride 25 mg/mL oral liquid were prepared by reconstituting commercially available Vancomycin Hydrochloride for Injection with sterile water for injection and then diluting with a mixture of equal volumes of Ora-Sweet and distilled water then placed in plastic bottles. Samples were analyzed for changes in color, taste and pH, as well as content. Samples were stored at both 4° C and 23° C, with sampling after 15, 30, 40, 50, 63 and 75 days. Results showed there were no notable changes in color, taste or pH stored at either temperature over the 75 day time period. Also, samples stored at 4° C were stable over the 75 day time period whereas those stored at 23° C were stable for up to 26 days.[9]

Table 6: Stability of vancomycin 25 mg/mL in plastic bottles stored at 4° and 23° C.

Temperature	Initial Concentration Remaining					
	Day 15	Day 30	Day 40	Day 50	Day 63	Day 75
4° C	25.73 (1.90)	24.65 (2.23)	25.35 (1.33)	25.41 (0.91)	25.11 (0.61)	26.37 (0.79)
23° C	25.16 (1.69)	23.43 (0.60)	22.69 (0.65)	23.02 (0.64)	22.71 (1.11)	19.69 (1.15)

Initial concentration for the 4° C samples was 25.77 (1.028) and for the 23° C samples was 24.74 (0.817).

Ziprasidone Mesylate 2.5 mg/mL Oral Suspension

Ziprasidone mesylate ($C_{21}H_{21}ClN_4OS \bullet CH_3SO_3H \bullet 3H_2O$, MW 563.09, Geodon®) for Injection is available in a single-dose vial as ziprasidone mesylate. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium.

Ziprasidone mesylate 2.5 mg/mL was prepared using Geodon for Injection. The injection was reconstituted and further diluted with Ora-Sweet. It was packaged in amber, plastic prescription bottles and stored at either room temperature or in a refrigerator. Samples were obtained at 0, 4, 8, 12, 24 hours and at 2, 3, 4, 7, 14, 21 and 42 days. Room temperature storage samples that were protected from light retained potency for up to 14 days; when stored in the refrigerator, they were stable for 6 weeks according to the article.[10]

Zonisamide 10 mg/mL Oral Suspension

Zonisamide ($C_8H_8N_2O_3S$, MW 212.23, Zonegran®) occurs as a white to off-white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL).[2] Zonegran is supplied for oral administration as capsules containing 25 mg, 50 mg or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

Zonisamide 10 mg/mL oral suspension was prepared by emptying the commercially available capsules of zonisamide 100 mg in a glass mortar. The vehicle (either Simple Syrup NF or methylcellulose 0.5% w/v solution) was added to volume with mixing. The preparation was packaged in amber plastic prescription containers and stored at 23-25° C and 3-5° C. Samples were analyzed initially and after 7, 14, 21, 28 days. The results show that at least 90% of the initial concentration of zonisamide remained intact in all suspensions throughout the study. There were no visible color or odor changes in any of the suspension. There was no observable microbial growth in the preparations stored under refrigeration; but there was significant microbial growth in the methylcellulose preparations stored at room temperature at 14, 21 and 28 days. In summary

and shown in Table 7, zonisamide in Simple Syrup NF suspensions was stable at both room and refrigerated temperature for at least 28 days. However, those in methylcellulose were stable for 28 days under refrigeration but only for 7 days at room temperature.[11]

Table 7: Stability of zonisamide 10 mg/mL in plastic bottles stored at 3-5° and 23-25° C .

Formula	Temp	% Initial Concentration Remaining			
Vehicle		Day 7	Day 14	Day 21	Day 28
Syrup	3-5°	102 (18)	100(4)	101 (14)	95 (19)
	23-25°	99 (2)	98 (15)	105 (9)	102 (11)
Methylcellulose	3-5°	99 (6)	92(6)	101 (3)	104 (7)
	23-25°	99 (9)	102 (1)	92 (15)	103 (6)

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Please circle the most appropriate answer for each of the following questions. There is only ONE correct answer per question.

1. Excipients that are in commercial dosage forms used for compounding, should be evaluated for what effects on the final preparation?

I. Safety
II. Stability
III. Efficacy

A. I only
B. III only
C. I and II only
D. II and III only
E. I, II and III

2. In which of the following preparations is the active drug NOT in solution?

A. Clonidine Hydrochloride 0.1 mg/mL Oral Liquid
B. Oseltamivir Phosphate 6 mg/mL Oral Liquid
C. Thioguanine 20 mg/mL Oral Liquid
D. Vancomycin 25 mg/mL Oral Liquid
E. Zonisamide 10 mg/mL Oral liquid

3. Which of the following preparations are "light-sensitive"?

I. Clonidine Hydrochloride
II. Levothyroxine Sodium
III. Oseltamivir Phosphate

A. I only
B. III only
C. I and II only
D. II and III only
E. I, II and III

4. Which of the studies had the largest "variability" in the study results?

A. Clonidine Hydrochloride
B. Glycopyrrolate
C. Levothyroxine Sodium
D. Vancomycin
E. Zonisamide

5. Which of the following factors are commonly affected by pH?

I. Solubility
II. Stability
III. Particle size

A. I only
B. III only
C. I and II only
D. II and III only
E. I, II and III

6. Which of the following ingredients may change to a slight pink color upon exposure to light?

A. Clonidine Hydrochloride
B. Levothyroxine Sodium
C. Melatonin
D. Oseltamivir Phosphate
E. Vancomycin

7. Which of the following injections used for compounding uses a cyclodextrin to solubilize the drug?

A. Clonidine Hydrochloride
B. Glycopyrrolate
C. Tadalafil
D. Vancomycin
E. Ziprasidone Mesylate

8. For which of the following preparations is the method of preparation included in the approved labeling of the commercial drug product?

A. Clonidine Hydrochloride
B. Levothyroxine Sodium
C. Melatonin
D. Oseltamivir Phosphate
E. Vancomycin

9. In which preparation vehicle and temperature was there reported microbial growth for the zonisamide?

I. Syrup, 3-5° C
II. Methylcellulose, 3-5° C
III. Methylcellulose, 23-25° C

A. I only
B. III only
C. I and II only
D. II and III only
E. I, II and III

10. Which of the preparations had the shortest "Beyond-Use Date"?

A. Clonidine Hydrochloride 0.1 mg/mL
B. Glycopyrrolate 0.5 mg/mL
C. Levothyroxine Sodium 25 µg/mL
D. Tadalafil 5 mg/mL
E. Thioguanine 20 mg/mL

11. My practice setting is:

A. Community-based
B. Managed care-based
C. Hospital-based
D. Consultant and other

12. The quality of the information presented in this article was:

A. Excellent B. Good C. Fair D. Poor

13. The test questions correspond well with the information presented.

A. Yes B. No

14. Approximately how long did it take you to read the Secundum Artem article AND respond to the test questions?

15. What topics would you like to see in future issues of Secundum Artem?

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