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STABILITY OF EXTEMPORANEOUSLY PREPARED ORAL LIQUID FORMULATIONS – Part V

GOALS AND OBJECTIVES

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

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

1. Discuss the factors involved in conducting a stability study.
2. Describe the beyond-use dates for ten different compounded pediatric formulations.
3. Discuss the different methods used for compounding oral liquids using commercially available vehicles.
4. List the three different types of stability of which compounding pharmacists should be aware.

INTRODUCTION

Most commercially available medications do not have a pediatric dosage form available and are not labeled for pediatric administration. However, many pediatric patients require specific doses that must be individualized by body weight or body surface area for administration of smaller-than-commercially available doses. Consequently, these medications must generally be prepared either at the time of administration by mixing with food or a palatable drink by a caregiver or compounded by a pharmacist for administration over a period of time.

One of the downsides to this situation is that stability information is frequently not available. Because of these concerns, there has been a concerted effort over the past 20 years to obtain as much stability information as possible by research studies in laboratories on the stability of these drugs in common oral vehicles. Ora-Plus®, Ora-Sweet® and Ora-Sweet® SF are the primary vehicles used in these research studies.

In a survey published in 2001, 233 hospitals received a four-page questionnaire designed to obtain the following information:[1]

1. drug formulations prescribed, but not dispensed due to lack of compounding and stability data
2. ten most frequently compounded drug formulations needing longer or better stability data
3. ten most frequently compounded drug formulations with adequate stability data

Over 100 drug formulations were listed as needing stability data. Some of the drugs on this list have now become commercially available, especially since financial incentives have been offered by the government. However, many more studies are needed to address all the drugs that are administered to pediatric patients.[1]

Most published research studies address the chemical stability of pediatric formulations. However, other aspects should also be considered, including the physical stability and microbiological stability of the compounded preparation.

STUDY DESIGNS

In general, the procedures involve the following steps:

1. Selection and development of the drugs to be tested and the formulation for the study (See Table 1).
2. Development and validation of a stability-indicating assay for the active drug in the fozrmulation.
3. Development of the study protocol, including containers, storage temperatures, etc.
4. Preparation of the study samples.
5. Pulling the initial samples and placing the containers in the appropriate storage conditions.
6. Pulling samples as indicated.
7. Analyzing the active drug.
8. Data analysis and presentation.

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TABLE 1

CONCENTRATIONS OF THE VARIOUS DRUGS IN THE STUDIES REPORTED IN THIS PAPER WERE AS FOLLOWS:

Drug	Concentration (mg/mL)
Benazepril hydrochloride	2
Levodopa/Carbidopa	5/1.25
Losartan potassium	2.5
Sotalol	5
Sulfasalazine	100
Theophylline	5
Thiamine hydrochloride	100
Tramadol	5
Ursodiol	25
Valganciclovir	60

STABILITY OF EXTEMPORANEOUS FORMULATIONS

Benazepril Hydrochloride

Benazepril hydrochloride ($C_{24}H_{28}N_2O_5$.HCl, MW 460.95, Lotensin®) occurs as a white to off-white crystalline powder that is soluble over 100 mg/mL in water and is also soluble in ethanol. Benazepril is supplied as tablets containing 5 mg, 10 mg, 20 mg and 40 mg of benazepril hydrochloride for oral administration. The tablets also contain colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5 mg, 10 mg and 20 mg tablets), hypromellose, iron oxides, lactose, magnesium stearate (40 mg tablets), microcrystalline cellulose, polysorbate 80, propylene glycol (5 mg and 40 mg tablets), starch, talc, and titanium dioxide.[2]

Benazepril hydrochloride 2 mg/mL oral suspension (150 mL) was prepared for the stability study by adding 75 mL of Ora-Plus to an amber polyethylene terephthalate (PET) bottle containing fifteen Lotensin 20 mg tables, and shaken for at least 2 minutes. The suspension was allowed to stand for a minimum of 1 hour. After standing, the suspension was shaken for a minimum of one additional minute. Then, 75 mL of Ora-Sweet was added to the bottle and shaken to disperse the ingredients. The suspension was refrigerated and stored for up to 30 days in the PET bottle with a child-resistant screw-cap closure. The suspension should be shaken prior to each use.

The results showed there was no significant loss during the study. A beyond-use date of up to 30 days can be used based upon this study.[2]

Levodopa/Carbidopa

Carbidopa ($C_{10}H_{14}N_2O_4.H_2O$, MW 244.24) occurs as a white to creamy white odorless or practically odorless powder. It is slightly soluble in water, freely soluble in 3 N hydrochloric acid, and practically insoluble in alcohol. It should be protected from light.

Levodopa ($C_9H_{11}NO_4$, MW 197.19) occurs as a white to off-white odorless crystalline powder. In the presence of moisture, it is rapidly oxidized by atmospheric oxygen and darkens. It is slightly soluble in water, freely soluble in 3 N hydrochloric acid, and insoluble in alcohol. It should be stored in a tight container and protected from light. Because it is unstable, it must be prepared in an acidic vehicle and the resultant preparation must be assigned a brief beyond-use date.

For the stability study, the suspension containing 5 mg/mL levodopa and 1.25 mg/mL carbidopa was prepared by pulverizing ten tablets (levodopa 100 mg and carbidopa 25 mg each) in a mortar. Two hundred mL of a 1:1 mixture of Ora Plus:Ora Sweet was prepared and a small portion of this vehicle added to the powder and levigated to form a smooth paste. Geometrically, the remaining vehicle was added to volume and mixed well. Shake the suspension thoroughly prior to each administration.

From this study, a beyond-use date of 6 weeks in the refrigerator and 4 weeks at room temperature can be used. The data obtained is shown in Table 2. The initial and final pH for the refrigerated temperature preparations was 4.41 and 4.46, respectively; for the room temperature preparations was 4.41 and 4.61, respectively.[3]

TABLE 2

PERCENT OF LEVODOPA-CARBIDOPA PREPARED IN ORA-PLUS:ORA SWEET AFTER STORAGE AT EITHER ROOM OR REFRIGERATED TEMPERATURE.[3]

Time (Days)	Refrigerated Temperature		Room Temperature	
	Levodopa	Carbidopa	Levodopa	Carbidopa
7	99.54	99.35	99.58	99.35
14	98.24	98.06	98.59	96.42
28	96.56	96.49	96.43	92.00
42	94.88	93.92	92.12	83.16
56	92.92	90.34	87.81	74.32
70	90.20	87.87	83.38	65.49
91	87.52	83.91	76.71	56.65

Losartan Potassium

Losartan potassium ($C_{22}H_{22}ClKN_6O$, MW 461.00, Cozaar®) occurs as a white to off-white free-flowing powder that is freely soluble in water, soluble in alcohols and slightly soluble in common organic solvents. Cozaar tablets contain either 25 mg, 50 mg or 100 mg of losartan potassium along with microcrystalline cellulose, hydrous lactose, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.[4]

The losartan potassium oral suspension (200 mL of a 2.5 mg/mL suspension) was prepared by adding 10 mL of purified water to a 240 mL amber polyethylene terephthalate (PET) bottle containing ten 50 mg Cozaar tablets. It was shaken for at least 2 minutes. This concentrate was allowed to stand for one hour and then shaken for at least one minute to disperse the tablet contents. Separately, a 1:1 volumetric mix of Ora-Plus and Ora-Sweet SF was prepared and about 190 mL of the mixture added to the tablet concentrate and shaken for one minute to disperse the ingredients. This prepared 200 mL of suspension.

From the results of the study, the suspension should be refrigerated and can be stored for up to 4 weeks. It should be shaken prior to each use and promptly returned to the refrigerator.[4]

Sotalol Hydrochloride

Sotalol hydrochloride ($C_{12}H_{20}N_2O_3S$.HCl, MW 308.82, Betapace®) is an anti-arrhythmic agent that occurs as a white to off-white powder that is freely soluble in water and soluble in alcohol and propylene glycol. It is stable in the pH range of 4 to 5.[1,4] The Betapace brand of sotalol hydrochloride tablets also contain microcrystalline cellulose, lactose, starch, stearic acid, magnesium stearate, colloidal silicon dioxide, and FD&C blue color #2.[5]

Sotalol hydrochloride 5 mg/mL oral liquid was prepared as follows. Sotalol hydrochloride tablets were pulverized to a fine powder. Geometrically, the Ora-Plus was incorporated and mixed to a fine powder. Sufficient Ora-Sweet was added to volume and mixed until uniform. The study results showed that these vehicles can be used for sotalol with an assigned beyond-use date of up to 91 days.[6]

The preparations had pH values of 4.30 and 4.29 initially and 4.34 and 4.34 at the end of study, respectively for the refrigerated and room temperature samples.

TABLE 3

STABILITY OF SOTALOL IN ORA-PLUS/ORA SWEET AT 4° C AND 25° C.[6]

Day	Percent of Initial Concentration Remaining 4° C	25° C
0 (mg/mL)	5.1	5.1
7	100.0	100.7
14	100.1	100.1
28	100.0	100.1
42	100.4	99.2
56	99.3	99.6
70	98.9	97.3
91	99.3	95.5

A second study has also been reported, as follows. To prepare 240 mL of a 5 mg/mL oral suspension, place five of the 240 mg sotalol hydrochloride tablets in a glass mortar and comminute them to a fine powder. Add about 5 mL of Ora-Plus (OP) and mix to form a smooth paste. Add about 115 mL of Ora-Plus in portions mixing well. Transfer to a calibrated 240 mL bottle. Rinse the mortar with small potions of Ora-Sweet (OS) or Ora-Sweet SF (OS-SF) and transfer to the calibrated bottle. Add additional Ora-Sweet or Ora-Sweet SF to volume and mix well.

An appropriate beyond-use date for this study formulation was up to 12 weeks. The percent of sotalol hydrochloride remaining after storage at either room or refrigerated temperature.[7]

The initial pH of the refrigerated temperature samples was 4.22 and 4.14 for the OP-OS and OP-OS-SF samples, respectively; the final pH of the samples was 5.33 and 5.27, respectively. The initial pH of the room temperature samples was 4.07 and 4.02 for the OP-OS and OP-OS-SF samples respectively; the final pH of the samples was 4.36 and 4.45, respectively.

TABLE 4

PERCENT SOTALOL REMAINING AFTER STORAGE FOR UP TO 12 WEEKS AT EITHER REFRIGERATED OR ROOM TEMPERATURE.[7]

Time (Weeks)	Refrigerated Temperature Ora Plus /Ora Sweet	Ora Plus /Ora Sweet SF	Room Temperature Ora Plus /OraSweet	Ora Plus /Ora SweetSF
1	102.0	111.0	99.7	103.0
2	104.0	101.0	101.0	100.0
3	100.0	101.0	91.1	103.0
4	103.0	102.0	100.0	102.0
5	102.0	103.0	99.2	107.0
12	107.0	112.0	107.0	111.0

Sulfasalazine

Sulfasalazine ($C_{18}H_{14}N_4O_5S$, MW 398.39) occurs as a bright yellow or brownish yellow, odorless, fine powder that melts at about 255° C with decomposition. It is very slightly soluble in alcohol (1 g in 2900 mL) and practically insoluble in water. It is soluble in aqueous solutions of alkali hydroxides. It should be protected from light.[1] Sulfasalazine 250 mg/5 mL was formerly manufactured by Pharmacia-Upjohn under the brand name of Azulfidine®.

The stability of a 100 mg/mL suspension of sulfasalazine was studied in a mixture of 50% Ora-Sweet and 50% Ora-Plus in amber glass, amber polyethylene terephthalate (PET-G) and amber polyvinylchloride (PVC) containers over 91 days at both room and refrigerated temperature. The sulfasalazine 100 mg/mL oral suspension were prepared by placing 20 sulfasalazine 500 mg tablets in a mortar and adding some of the vehicle (Ora-Plus:Ora-Sweet 1:1) to cover the tablets and allowing them to set for 20-30 minutes. Using a pestle, the softened tablets were levigated to a smooth paste. Geometrically, the remainder of the vehicle was added to 100 mL and mixed well.[8]

The suspensions were initially thick and opaque with a creamy brownish yellow or light orange color and brownish yellow particles with no change throughout the study. No caking was observed in any of the containers and re-dispersion was easily accomplished. The pH was about 4.4 and did not change significantly throughout the study period.

The authors concluded that suspensions of 100 mg/mL sulfasalazine in a mixture of 1:1 Ora-Sweet and Ora-Plus is stable for 91 days when stored in amber glass, amber PET, or amber PVC containers at both room and refrigerated temperatures.[8]

TABLE 5

PERCENT SULFASALAZINE REMAINING AFTER STORAGE FOR UP TO 91 DAYS AT EITHER REFRIGERATED OR ROOM TEMPERATURE.[8]

Study Day	Amber PVC 23° C	4° C	Amber PET-G 23° C	4° C	Amber Glass 23°C	4° C
Initial	100.29	103.04	96.93	96.64	100.34	101.50
2	100.70	100.16	104.20	101.08	99.47	100.05
7	101.42	100.29	100.72	100.89	100.33	100.74
14	105.06	100.50	105.08	104.04	101.77	100.36
21	103.89	104.69	103.77	102.05	101.78	104.37
28	103.11	100.09	103.84	106.05	103.01	104.96
42	105.08	103.11	105.01	106.62	104.93	105.60
91	103.87	99.98	104.62	104.95	102.19	101.82

Theophylline

Theophylline anhydrous ($C_7H_8N_4O_2$, MW 180.18) occurs as a white odorless crystalline powder with a bitter taste. It is also available as the monohydrate. Theophylline is only slightly soluble in water at pH 7 and the aqueous solubility increases with an increase in pH. It is sparingly soluble in alcohol. Two molecules of theophylline in combination with one molecule of ethylenediamine forms aminophylline, which is more soluble in water than theophylline. Theophylline occurs naturally and is a component of tea. Theophylline products that are commercially available include extended release oral capsules, tablets, extended release tablets and solutions. The solutions generally contain alcohol in concentrations from 5% to 20%. The compounded formula here can be used when an oral liquid containing no alcohol is needed.[9]

The theophylline 5 mg/mL oral liquid was prepared by placing the anhydrous theophylline powder (300 mg) or a 300 mg extended release theophylline tablet in a suitable mortar. A few milliliters of Ora-Plus was added and mixed to form a

smooth paste. Geometrically, the remainder of the 30 mL Ora-Plus was added and mixed well. Finally, the Ora-Sweet or Ora-Sweet SF was added to 60 mL volume and mixed well. The study results showed that a beyond-use date of up to 90 days can be used for this preparation. The initial pH of all the preparations from both the powder or tablets was 4.32.[9]

TABLE 6

PERCENT THEOPHYLLINE REMAINING AFTER STORAGE FOR UP TO 90 DAYS AT ROOM TEMPERATURE PREPARED FROM EITHER POWDER OR TABLETS.[9]

Time (days)	Prepared from Powder		Prepared from Tablets	
	Ora Plus /Ora Sweet	Ora Plus /Ora Sweet SF	Ora Plus /OraSweet	Ora Plus /Ora SweetSF
7	101.59	100.03	100.24	100.27
14	100.03	99.87	100.38	99.93
30	100.91	100.0	100.4	100.26
60	100.52	100.39	99.85	99.92
90	100.3	100.26	100.21	99.81

Thiamine

Thiamine hydrochloride ($C_{12}H_{17}ClN_4OS.HCl$, MW 337.27, Vitamin B1) occurs as white crystals or as a white crystalline powder, usually with a slight, characteristic odor. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. It melts at about 248º C with some decomposition. It is freely soluble in water, soluble in glycerin and slightly soluble in alcohol. Thiamine is relatively stable in solutions in the pH range of 3.5 to 5.

The study preparations for 100 mL of a 100 mg / ml thiamine oral liquid were prepared by placing 10 g of thiamine hydrochloride powder in a mortar. A few milliliters of a 1:1 mixture of Ora-Plus:Ora-Sweet was added and mixed to form a smooth paste. Geometrically, sufficient Ora-Plus:Ora-Sweet to 100 mL was added and mixed well. For the study, the preparations were stored in amber, plastic prescription bottles. Physical characteristics studied included pH, odor, taste, color, viscosity, precipitation and ease of resuspension.[10]

Thiamine 100 mg / mL was found to be stable when prepared in a 1:1 mixture of Ora-Sweet and Ora-Plus, both physically and chemically, for up to 91 days, both at room temperature and under refrigeration when packaged in amber, plastic prescription bottles.[10]

Tramadol

Tramadol hydrochloride ($C_{16}H_{25}NO_2.HCl$, MW 299.84, Ultram®) is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The partition coefficient is 1.35 at pH 7.

Tramadol is commercially available as 50 mg film-coated tablets and in combination with acetaminophen. The tablets also contain corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax.

The suspensions were prepared by counting out six 50 mg Ultram tablets. The tablets were pulverized in a glass mortar to a fine powder. Thirty mL of Ora-Plus was mixed with 30 mL of either strawberry syrup or Ora-Sweet SF and vigorously stirred. The mortar was rinsed with about 15 mL of the vehicle and mixed well. The contents were transferred to a 60 mL calibrated amber plastic prescription bottle. The mortar was rinsed with about 15 mL of the vehicle mixture and transfer and the contents added to the bottle. This was repeated as necessary with sufficient vehicle to final volume and mixed well.

The study results showed that all formulations were stable for up to 90 days. The initial and final pH values at both temperatures ranged from 4.30 to 4.34.[11]

TABLE 7

PERCENT TRAMADOL HYDROCHLORIDE REMAINING AFTER STORAGE FOR UP TO 90 DAYS AT EITHER REFRIGERATED OR ROOM TEMPERATURE.[11]

Time (days)	Refrigerated Temperature		Room Temperature	
	Ora Plus /Ora Sweet SF	Ora Plus /Strawberry	Ora Plus /OraSweet SF	Ora Plus /Strawberry
7	100.62	100.4	100.79	100.2
14	100.28	99.28	100.59	100.0
30	100.39	99.51	100.51	99.94
60	99.57	100.75	100.75	99.04
90	100.98	100.79	100.79	100.49

Ursodiol 25 mg/mL

Ursodiol USP ($C_{24}H_{40}O_4$, MW 392.57, ursodeoxycholic acid, Urso®, Actigall®) occurs as a white or almost white, crystalline powder. It is practically insoluble in water and freely soluble in alcohol. Ursodiol capsules (Actigall) also contain colloidal silicon dioxide, ferric oxide, gelatin, magnesium stearate, cornstarch, and titanium dioxide. Ursodiol tablets (URSO 250) contain microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, ethylcellulose, dibutyl sebacate, carnauba wax, hydroxypropyl methylcellulose, polyethylene glycol 3350, polyethylene glycol 8000, cetyl alcohol, sodium lauryl sulfate, and hydrogen peroxide.[12]

The Ursodiol 25 mg / mL oral liquid was prepared by counting out ten 300 mg ursodiol capsules. The contents of the capsules were emptied into a glass mortar and comminuted well. Ten mL of glycerin was added and the mixture levigated to form a smooth paste. Sixty mL of Ora-Plus was added geometrically with mixing until a smooth mixture was obtained. The mixture was transferred to a calibrated 120 mL amber bottle. A small quantity of orange syrup was added to the mortar to rinse the remaining drug mixture and added to the bottle. Sufficient orange syrup was added to volume and mixed well.

From the results of this study, a beyond-use date of up to 60 days can be used for this preparation. The initial and final pH values for both temperatures did not vary outside the range of pH 3.5 to pH 3.7.[13]

TABLE 8

STABILITY OF URSODIOL 25 MG/ML IN ORAL LIQUID AT ROOM AND REFRIGERATED TEMPERATURES.[13]

Time (days)	Refrigerated Temp.	Room Temp.
7	97.1	98.1
15	102.2	104.7
30	103.0	106.7
45	107.1	107.2
60	103.3	108.4

Valganciclovir

Valganciclovir hydrochloride ($C_{14}H_{22}N_6O_5$.HCl, MW 390.82, Valcyte®) occurs as a white to off-white crystalline powder. It has a solubility of 70 mg / mL in water at 25º C at a pH of 7.0, and an n-octanol / water partition coefficient of 0.0095 at pH 7.0. The Valcyte 450 mg tablets also contain microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film coating contains Opadry Pink.[14]

The valganciclovir 60mg / ml study preparation was formulated by placing 16 valganciclovir 450 mg tablets in a mortar and pulverizing to a fine powder. Small portions of Ora-Plus were added followed by levigation to form a smooth paste. Ora-Plus was added to a volume of 60 mL with thorough mixing. The mixture was transferred to a calibrated 120 mL amber glass bottle. The mortar was rinsed with 10 mL portions of Ora-Sweet and added to the container. This was continued until 120 mL of final mixture was obtained and then it was mixed thoroughly. A beyond-use date of up to 35 days can be used for this preparation. The initial and final pH of the preparations was 3.8 and did not change during the study.[15]

TABLE 9

PERCENT VALGANCICLOVIR HYDROCHLORIDE REMAINING AFTER STORAGE FOR UP TO 35 DAYS AT EITHER REFRIGERATED OR ROOM TEMPERATURE.[15]

Time	Refrigerated Temp.		Room Temp.	
(days)	30 mg/mL	60 m g/mL	30 mg/mL	60 mg/mL
10	97.0	98.5	93.6	97.1
20	94.0	96.9	90.9	95.2
35	93.4	95.8	90.7	94.2

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