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STABILITY OF EXTEMPORANEOUSLY PREPARED ORAL LIQUID FORMULATIONS - PART IV

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 legislative and regulatory activities involving medications for pediatric patients.
2. describe the general study designs for stability studies used to aid in establishing beyond-use dates.
3. discuss the care to be used in terminology related to assigning beyond-use dates.
4. observe the presented tabular data and determine a reasonable beyond-use date for the presented drugs.

INTRODUCTION

On January 4, 2002, the President signed into law S.1789, the Best Pharmaceuticals for Children Act, as P.L. 107-109. This legislation actually reauthorizes the pediatric studies provision of the Food and Drug Administration Modernization Act of 1997 (FDAMA97). It encourages pharmaceutical companies, by extending their market exclusivity, to conduct pediatric studies of new and already marketed drugs used in pediatric populations but are not labeled for such use.

This new legislation provides several avenues by which drugs already on the market can be tested in children. These involve (1) the patent holder doing the testing and gaining an additional six months exclusivity, (2) if off patent and manufacturers reject a request from the FDA to test it in children, the Secretary of HHS may ask the NIH to undertake the research under contract, and (3) if the holder of a patented drug refuses to test the drug in children, the Secretary can ask the Foundation for the NIH to test the drug with funds from the private sector; in this case, the additional exclusivity will not be allowed to the patent-holder.

As is evident, there is concern about the lack of availability of appropriate pediatric dosage forms. In the past and present, pharmacists routinely prepare dosage forms for children, either from commercially available dosage forms (tablets, capsules, injections) or from USP grade substances. The question that commonly arises relates to the stability of the active ingredient in the selected vehicle. This is Part IV in a series designed to summarize stability studies that have been conducted in different vehicles, including either Ora-Sweet®, Ora-Sweet® SF, Ora-Plus®, or their combinations; and methylcellulose and syrup combinations.

STUDY DESIGNS

Most stability studies result from questions involving commonly used dosages in children. It is routine to study only one, or maybe two, concentrations of a drug in the selected vehicles. Temperatures commonly used in these studies include room temperature and/or refrigerated temperature. The preparations are generally placed in light-resistant containers and sampled at pre-determined intervals. The preparations may be prepared from either commercial dosage forms or from USP-grade substances.

Stability-indicating assays, generally high-performance liquid chromatography, are routinely developed, validated and used for these studies. A standard cutoff of 90% of the initial concentration remaining is generally used in assigning a beyond-use date. It is customary to provide the actual analyzed concentration at the initial time point and the remaining time intervals are expressed as a percent of the original drug remaining. In the actual studies, the standard deviations must be provided to assist in evaluating the cutoff time for the recommended beyond-use date.

Loyd V. Allen, Jr., Ph.D., R.Ph.
- Professor Emeritus, University of Oklahoma College of Pharmacy
- Editor in Chief, International Journal of Pharmaceutical Compounding
- Dr. Allen is not affiliated with Paddock Laboratories Inc.

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Table 1 provides the concentrations of the various drugs used in the studies discussed in this issue. The vehicles studied vary and include Ora-Sweet, Ora-Sweet SF and Ora-Plus, either individually or in combination (usually a 1:1 mix of the flavored Ora-Sweet or Ora-Sweet SF in combination with Ora-Plus) and mixtures of simple syrup with 1% methylcellulose solution and simple syrup with citric acid added. Generally the methylcellulose 1% solution contained methylcellulose 4000 cps (1 g), methylparaben (20 mg), propylparaben (10 mg) and purified water.

TABLE 1

CONCENTRATIONS OF DRUGS USED IN THE STUDIES WERE AS FOLLOWS:

Drug	Concentration (mg/mL)
Amphetamine (Adderal®)	1
Amiodarone	5
Amlodipine besylate	1
Atenolol	2
Dapsone	2
Ganciclovir	100
Lamotrigine	1
Nifedipine	4
Propylthiouracil	5
Sildenafil	2.5

It should be noted that there can be confusion in the way stability studies are referred to in the literature. For example, if a study was conducted for only 7 days and at the end of that study timeframe, 99.5% of the active drug remained, it may be presented as the drug is "stable for 7 days". Actually, the drug is stable for "at least 7 days". Therefore, it is important to review the original article when establishing the beyond-use date for the compounded preparation. Additional comments will be discussed in Part V of this series.

STABILITY OF EXTEMPORANEOUS FORMULATIONS

Amphetamine (Adderall)

Adderall® is the brand name for a product that contains equal milligram quantities of d-amphetamine saccharate, d,l-amphetamine aspartate, d-amphetamine sulfate, and d,l-amphetamine sulfate, resulting in a 3:1 ratio of dextroamphetamine to levoamphetamine. It is available in double-scored tablets of different strengths and is frequently prescribed to treat attention deficit hyperactivity disorder (ADHD). Amphetamine sulfate occurs as a white, odorless, crystalline powder with a slightly bitter taste. It is freely soluble in water, and slightly soluble in alcohol.[1,2]

The formulation was prepared using a 1:1 mixture of Ora-Sweet and Ora-Plus. The concentration was 1 mg/mL and the commercial Adderall 10 mg tablets were used in the preparation. The storage temperature was 25º C. The analytical method used was gas chromatography-mass spectrometry and was developed to analyze for the isomers.

There was no significant loss of either amphetamine isomer during the 30-day study and the ratio of the dextroamphetamine to levoamphetamine was consistent in all vehicles. The study also included the drug in Ora-Sweet only and Ora-Plus only with no significant loss in either single vehicle. The authors conclude that the Adderall suspension was stable for at least 30 days when stored at room temperature.

TABLE 2

STABILITY OF D-AMPHETAMINE AND L-AMPHETAMINE IN ADDERALL 1 MG/ML ORAL LIQUID IN A 1:1 MIXTURE OF ORA-SWEET AND ORA-PLUS AT ROOM TEMPERATURE

Time	D-amphetamine Conc.	L-amphetamine Conc.
Initial (µg/mL)	519.4	166.7
Day 10	96.4%	113.0%
Day 20	95.4%	112.0%
Day 30	92.0%	112.9%

Amiodarone Hydrochloride

Amiodarone hydrochloride, used as an antiarrhythmic in infants and children unresponsive to conventional therapy, is available only as a 200 mg tablet. Amiodarone hydrochloride occurs as a white or almost white, fine crystalline powder that is very slightly soluble in water and sparingly soluble in alcohol. It should be protected from light.

This stability study used the tablets to prepare a suspension of 5 mg/mL concentration using a 1:1 mixture of Ora-Sweet/Ora-Plus and Ora-Sweet SF/Ora-Plus. The pH was adjusted with sodium bicarbonate to the range of pH 6 to 7. The source of the drug in this study was Cordarone® 200 mg commercial tablets which also contain colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch and FD&C Red 40. Samples were stored at both room and refrigerated temperatures. Room temperature samples were stable for 42 days and refrigerated samples were stable for 91 days.[2,3]

The initial pH values were 6.30 and 6.29 for the preparations and the final pH values were 6.34 for all preparations except the Ora-Sweet SF/Ora Plus which was 6.32.

TABLE 3

STABILITY OF AMIODARONE HYDROCHLORIDE 5 MG/ML AT TWO TEMPERATURES

	% Initial Concentration Remaining			
	25° C		4° C	
Day	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus
0 (mg/mL)	5.17	5.00	5.01	5.02
7	101.23	101.09	100.46	101.22
14	99.89	100.16	99.32	99.97
28	97.93	98.00	97.97	97.20
42	93.51	93.83	96.69	96.97
56	91.64	91.21	94.91	94.76
70	89.28	89.01	93.14	93.62
91	87.63	86.82	92.67	92.78

Amlodipine besylate

Amlodipine besylate is a dihydropyridine calcium antagonist used in treating pediatric patients with hypertension. Amlodipine besylate occurs as a white or almost white powder that is slightly soluble in water and sparingly soluble in dehydrated alcohol. It should be protected from light.

In this study, a suspension using Norvasc® 5 mg tablets in a vehicle of 1:1 Ora-Sweet/Ora-Plus or 1:1 simple syrup with 1% methylcellulose solution was prepared at a concentration of 1 mg/mL, packaged and stored at both

room and refrigerated temperatures. Norvasc brand tablets also contain microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate and magnesium stearate.

The results of the study show that amlodipine besylate is stable in both sets of vehicles at room temperature for at least 56 days and at refrigerated temperature for at least 91 days. The initial pH was 4.58 and the final pH was 4.61 and 4.59 for room and refrigerated temperatures, respectively, in the Ora-Sweet/Ora-Plus; the final pH was 6.50 and 6.69 for the methylcellulose: syrup vehicles, also at room and refrigerated temperatures, respectively.[2,4]

The methylcellulose:syrup formulations settled slightly faster than the Ora vehicles but both resuspended easily after shaking.

TABLE 4

STABILITY OF AMLODIPINE 1 MG/ML SUSPENSIONS AT TWO TEMPERATURES

% Initial Concentration Remaining

	Ora-Sweet/Ora-Plus		1% Methylcellulose/Syrup	
Day	25° C	4° C	25° C	4° C
0 (mg/mL)	0.99	1.03	1.05	1.02
7	100.27	99.99	99.21	100.21
14	99.05	99.53	98.72	99.63
28	98.13	99.19	97.27	99.17
42	96.62	98.84	94.76	98.47
56	95.47	97.86	92.39	97.21
70	93.11	97.03	89.67	96.92
91	90.72	95.87	87.63	94.27

Atenolol

Atenolol is a cardioselective beta-adrenergic antagonist that is not available as an oral liquid. Atenolol occurs as a white or practically white, odorless powder that is slightly soluble in water and sparingly soluble in alcohol. In this study, atenolol powder or tablets was prepared at a concentration of 2 mg/mL in vehicles of Ora-Sweet, Ora-Sweet SF and Ora-Plus; as well as Roxane® Diluent consisting of 1% ethanol, 0.05% saccharin in a cherry-flavored, 33% polyethylene glycol 8000 and purified water. Tenormin® brand tablets also contain magnesium stearate, microcrystalline cellulose, povidone and sodium starch glycolate.

Atenolol was found to not be stable in Ora-Sweet. The authors recommend atenolol in Ora-Sweet SF as the vehicle where it was most stable for at least 90 days or in the Roxane Diluent where it was stable for up to 40 days.[2,5]

Dapsone

Dapsone is used in both adult and pediatric patients in the prophylaxis of Pneumocystis carinii pneumonia (PCP) and for the treatment of PCP, lupus, leprosy and Kaposi sarcoma. Dapsone occurs as a white or creamy white, crystalline odorless powder with a slightly bitter taste. It is very slightly soluble in water and freely soluble in alcohol. Dapsone tablets also contain colloidal silicone dioxide, magnesium stearate, microcrystalline cellulose and corn starch.

Commercial Dapsone tablets (25 mg) were used to prepare the suspensions in a mixture of 1:1 Ora-Sweet/Ora-Plus for a nominal concentration of 2 mg/mL or in a vehicle containing 2% citric acid in purified water mixed 1:3 with simple syrup. The preparations were stored at both room and refrigerated temperatures.

The results show that the suspension was stable at both temperatures for at least 91 days in all the vehicles studied. The pH values for the Ora vehicles were 4.30 initially and 4.34 after storage at either temperature for 91 days and 2.80 initially and 2.79-2.84 after 91 days in the citric acid:syrup vehicle.[2,6]

TABLE 5

STABILITY OF DAPSONE 2MG/ML SUSPENSIONS AT TWO TEMPERATURES

% Initial Concentration Remaining

	Ora-Sweet/Ora-Plus		2% Citric Acid: Syrup (1:3)	
Day	25° C	4° C	25° C	4° C
0 (mg/mL)	2.08	2.01	2.00	2.02
7	101.72	100.73	101.17	101.43
14	100.89	100.55	100.10	100.97
28	100.21	100.11	100.03	100.20
42	100.02	100.09	99.83	99.97
56	99.64	99.22	98.23	99.18
70	98.28	98.71	97.80	97.84
91	97.61	98.14	95.94	96.98

Ganciclovir

Ganciclovir is used in the treatment of infections with Epstein-Barr virus and is the antiviral agent of choice for the prophylaxis and treatment of cytomegalovirus infections in immunocompromised patients. Ganciclovir occurs as a white to off-white crystalline powder with a solubility in water of about 2.6 mg/mL. Ganciclovir contains not more than 6.0% water and is extremely hygroscopic. If the powder is used for compounding, the water content needs to be considered.

It is commercially available as a lyophilized injection and as 250 and 500 mg capsules but not as an oral liquid. Ganciclovir capsules also contain croscarmellose sodium, magnesium stearate and povidone.

The authors prepared 100 mg/mL ganciclovir in Ora-Sweet only or Ora-Sweet SF only. The preparations were stored at room temperature. The drug was demonstrated to be stable for 123 days at room temperature. The pH of the formulations was approximately 4.5 and remained unchanged throughout the study period.[2,7]

TABLE 6

STABILITY OF GANCICLOVIR 100 MG/ML SUSPENSIONS AT ROOM TEMPERATURE

% Initial Concentration Remaining

Time (Days	Ora-Sweet	Ora-Sweet SF
0 (mg/mL)	97.2	100.6
15	96.7%	102.0%
35	99.3%	102.3%
60	96.0%	101.5%
91	100.8%	101.9%
123	99.8%	104.1%

Lamotrigine

Lamotrigine is used as adjunctive therapy for partial seizures. Lamotrigine occurs as a white to pale cream-colored powder that is very slightly soluble in water (0.17 mg/mL) and slightly soluble in 0.1 M HCl. The tablets also contain lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, FD&C Yellow No. 6 Lake (100 mg tablet); ferric oxide, yellow (150 mg tablet) and FD&C Blue No. 2 Lake (200 mg tablet).

It is commercially available only as a compressed tablet. The authors used the tablets to prepare suspensions with 1:1 mixtures of Ora-Sweet/Ora-Plus or Ora-Sweet SF/Ora-Plus at nominal concentrations of 1 mg/mL. The preparations were stored at both room and refrigerated temperatures. The results showed the lamotrigine suspensions to be stable throughout the 91 day study period at both temperatures. The initial pH values were 4.6 and 4.5 for the Ora-Sweet/Ora-Plus and Ora-Sweet SF/Ora-Plus, respectively.[2,8]

TABLE 7

STABILITY OF LAMOTRIGINE 1 MG/ML SUSPENSION AT TWO TEMPERATURES

% Initial Concentration Remaining

	4° C		25° C	
Day	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus	Ora-Sweet /Ora-Plus	Ora-Sweet SF /Ora-Plus
0 (mg/mL)	1.02	1.02	1.03	1.00
7	100.0	101.4	101.6	101.4
14	101.3	100.5	101.5	101.0
28	100.2	100.0	100.9	100.2
42	99.9	100.9	99.8	100.7
56	100.9	99.7	99.4	99.8
70	100.0	100.6	100.0	99.6
91	99.7	99.6	99.8	99.4

Nifedipine

Nifedipine is used in the treatment of hypertension in pediatric patients. It is available as sustained-release tablets and liquid-filled capsules. Consequently, a liquid dosage form is needed for pediatric patients. Nifedipine occurs as a yellow powder that is affected upon exposure to light. It is practically insoluble in water.

In this study, the capsules were used to prepare the suspensions at a concentration of 4 mg/mL using vehicles of 1:1 Ora-Sweet/Ora-Plus and 1% methylcellulose/simple syrup. The capsules were emptied of about 95% of the nifedipine using the following procedure. The top of the capsule was punctured with one needle to create a vent. Another needle attached to a syringe was used by inserting it through the bottom of the capsule and extracting the liquid by pulling back on the plunger of the syringe. The needle bevel was positioned close to the edge of the capsule and when a bubble first appeared in the syringe, the operator paused for about 5 seconds, then continued withdrawing the plunger. This was repeated twice. The drug and vehicle were thoroughly mixed. The preparations were stored at both room and refrigerated temperatures.

The results showed that the preparations were stable for up to 3 months at either temperature. There was no significant change in the pH values in any of the vehicles at the end of the 91 day study period.[2,9]

TABLE 8

STABILITY OF NIFEDIPINE 4 MG/ML SUSPENSIONS AT TWO TEMPERATURES

% Initial Concentration Remaining

	Ora-Sweet/Ora-Plus		1% Methylcellulose/Syrup	
Day	25° C	4° C	25° C	4° C
0 (mg/mL)	4.0	4.1	4.0	4.1
7	100.0	100.6	100.2	101.2
14	100.1	100.1	100.1	100.0
28	100.0	100.3	100.2	99.1
42	100.2	99.4	99.9	99.3
56	100.0	99.6	100.1	98.9
70	99.9	99.1	100.0	98.5
91	100.1	98.9	100.0	97.4

Propylthiouracil

Propylthiouracil is used in the treatment of hyperthyroidism in pediatric patients. It is available as a 50 mg tablet but not in an oral liquid dosage form. Propylthiouracil occurs as a white, powdery, crystalline substance with an appearance and touch similar to starch and it has a bitter taste. It is slightly soluble in water and sparingly soluble in alcohol.

This study utilized the 50 mg commercial tablets to prepare suspensions with a 1:1 mixture of Ora-Sweet/Ora-Plus or 1% methylcellulose/simple syrup at a concentration of 5 mg/mL. The suspensions were stored at both room and refrigerated temperatures. The results of the study showed that both vehicle formulations stored at room temperature were stable for 70 days and those stored at refrigerated temperature were stable for 91 days [2,10]

TABLE 9

STABILITY OF PROPYLTHIOURACIL 5 MG/ML SUSPENSIONS AT TWO TEMPERATURES

% Initial concentration Remaining

	Ora-Sweet/Ora-Plus		1% Methylcellulose/Syrup	
Day	4° C	25° C	4° C	25° C
0 (mg/mL)	5.1	5.1	5.1	5.2
7	100.4	100.7	100.3	100.2
14	99.9	99.8	99.6	99.7
28	99.5	98.9	99.4	99.0
42	99.4	97.6	98.5	96.6
56	98.7	96.2	95.3	95.8
70	97.3	93.9	97.1	93.4
91	96.0	91.7	95.6	91.6

Sildenafil

Sildenafil is used in the treatment of pulmonary hypertension. Sildenafil has been demonstrated to be effective in infants and children experiencing pulmonary hypertension. It is only commercially available in 25, 50 and 100 mg tablets. An oral liquid dosage form at 2.5 mg/mL was prepared using the tablets and a 1:1 mixture of Ora-Sweet/Ora-Plus and a mixture of 1% methylcellulose/simple syrup 1:1. The preparations were stored at both room and refrigerated temperatures. The results show that the preparations were stable at both temperatures throughout the 91 day study period. The pH did not change during the study nor was there any change in odor or physical appearance.[2,11]

TABLE 10

STABILITY OF SILDENAFIL CITRATE 2.5 MG/ML SUSPENSIONS AT TWO TEMPERATURES

Percent of initial concentration remaining

	Ora-Sweet/Ora-Plus		1% Methylcellulose/Syrup	
Day	4° C	25° C	4° C	25° C
0 (mg/mL)	2.5	2.5	2.6	2.5
7	100.5	100.1	99.3	98.9
14	99.6	99.2	99.6	99.4
28	98.6	99.8	98.2	98.9
42	99.9	99.3	98.6	99.4
56	99.6	99.7	99.3	98.7
70	98.9	98.3	98.6	98.4
91	98.7	98.5	98.8	98.6

SUMMARY

In summary, it appears that Adderall (1 mg/mL in Ora-Sweet/Ora-Plus) is stable for at least 30 days at 25° C; amiodarone (5 mg/mL in Ora-Sweet/Ora-Plus and Ora-Sweet SF/Ora-Plus) is stable for 42 days at 25° C and 91 days at 4° C; amlodipine besylate (1 mg/mL in Ora-Sweet/Ora-Plus and 1% methylcellulose/simple syrup) is stable for 56 days at 25° C and 91 days at 4° C; atenolol 2 mg/mL in Ora-Sweet SF only for 90 days at 25° C and in Roxane Diluent for 40 days at 25° C; dapsone (2 mg/mL in Ora-Sweet/Ora-Plus and 2% citric acid solution/syrup 1:3) for 91 days at both room 25°and refrigerated 4° temperatures; ganciclovir (100 mg/mL in Ora-Sweet only or Ora-Sweet SF only) for 123 days at 25° C; lamotrigine (1 mg/mL in Ora-Sweet/Ora-Plus and Ora-Sweet SF/Ora-Plus) was stable for 91 days at both room and refrigerated temperatures; nifedipine (4 mg/mL in Ora-Sweet/Ora-Plus and 1% methylcellulose/simple syrup) for 3 months at both room and refrigerated temperatures; propylthiouracil (5 mg/mL in Ora-Sweet/Ora-Plus and 1% methylcellulose/simple syrup) for 70 days at 25° and 91 days at 4° C.; and sildenafil (2.5 mg/mL in Ora-Sweet/Ora-Plus and 1% methylcellulose/syrup) for 91 days at both temperatures.

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