



Secundum Artem

*Current & Practical Compounding
Information for the Pharmacist.*

STABILITY OF EXTEMPORANEOUSLY PREPARED PEDIATRIC FORMULATIONS USING ORA-PLUS WITH ORA-SWEET AND ORA-SWEET SF - PART I

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INTRODUCTION

The most commonly used oral dosage forms today include tablets and capsules. Many patients cannot swallow these products easily so alternate formulations must be prepared, or compounded, by the pharmacist. When a modification is made to a commercial dosage form or when a new formulation is prepared, the pharmacist must be aware of its stability and should be able to project a reasonable expiration date.

Stability is defined as the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of manufacture.¹ The USP (Chapter <1191> "Stability Considerations in Dispensing Practice") describes five different types of stability that fall within the responsibilities of the pharmacist, including chemical, physical, microbiological, therapeutic and toxicological.¹ The types of stability addressed here include chemical, where "each active ingredient retains its chemical integrity and labeled potency, within the specified limits", and physical, where the "original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained".¹

Vehicles commonly used for extemporaneous compounding must be designed to enhance patient compliance and product compatibility and stability. Patient compliance depends partially upon how the product tastes, smells, feels, and looks. The selection of the vehicle also depends on the projected stability and compatibility of the active ingredient in the new environment, including pH, buffers, sucrose/sweetener concentration and the presence of water, alcohol and other liquids, flavoring components, preservatives, etc.

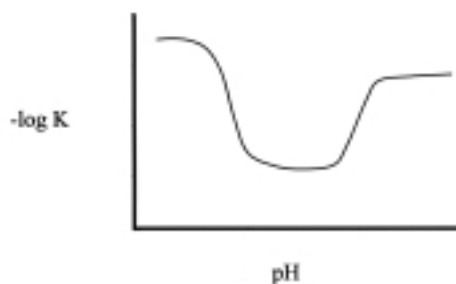
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STABILITY

Many drugs that are commonly used today are stable in the pH range of about 3-6. This information can be obtained by looking at a sample pH:degradation constant profile (See Figure 1). The lowest portion of the plot is the area of slowest degradation, or maximum stability. Many vehicles used in the past have been fruit syrups which are slightly acidic, such as cherry, orange, coke or raspberry syrups, etc. When neutral vehicles were required, regular simple syrup or tolu balsam syrup were used. One difficulty with using fountain syrups or syrups of undetermined or undefined composition is the potential interaction of any of the ingredients with the active drug substance. Some components of various syrups, flavors, etc. can adversely affect the stability of active drugs. Consequently, it is generally better practice to keep the formulation as simple as possible and to use vehicles of known composition.

Factors affecting stability include temperature, radiation, light, air and humidity. Additional factors may include such factors as particle size, pH, water and other solvents, container properties and the pres-

Figure 1: pH vs log K profile. The lowest area on the graph corresponds to the area of greatest stability, or the slowest degradation of the drug.



ence of other chemicals. The pharmacist's responsibility in the area of drug stability includes rotating stock and observing expiration dates, storage of the products under the recommended environmental conditions, observing products for evidence of instability, the proper treatment of products subjected to additional manipulations such as repackaging, dilution or mixing, and informing and educating the patient.¹

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Another potential problem involves the source of the active drug. The best source is the pure drug. If the pure drug substance is not available, it is common practice to use injectables, tablets, capsules or other dosage forms to obtain the active drug. Where this is necessary, the presence of excipients in the dosage form should be considered relative to the overall stability of the product.

A consideration not generally addressed by physical and chemical stability studies of extemporaneous compounds is the question of microbiological stability. Concentrated syrups have high osmolality which provides a preservative effect. Elixirs and similar preparations are preserved by their alcohol concentrations or by a combination of sucrose, alcohol and other preservatives. Commercial vehicles generally are preserved by the addition of a suitable preservative in their formulation. Microbiological stability was not a consideration in this study. These preparations should be microbiologically stable because no significant dilution of the vehicle occurred, and the vehicles contained antimicrobials.

STABILITY STUDY DESIGN

The stability data presented in this and subsequent *Secundum Artem* issues resulted from a two year long stability study involving thirty different drugs and their stability as 1:1 mixtures of Ora Sweet:Ora Plus and Ora Sweet SF:Ora Plus.

A survey mailed to community and hospital pharmacies was used to determine the active drugs and concentrations to be studied. The products and concentrations most often mentioned by these pharmacists resulted in a frequency list and, from this list, thirty drugs and their most frequently mentioned concentration in extemporaneously compounded oral liquids were selected for the overall study. Ten of these are presented in this issue of *Secundum Artem*.

For each drug and each vehicle, approximately 800 mL of product was prepared. Sufficient powder was weighed, or a sufficient number of tablets/capsules was obtained to provide the active ingredient. The tablets were pulverized, or capsules emptied, and the powder comminuted in a mortar with a pestle. A portion of the vehicle was used

to levigate the powder and a uniform paste prepared. Additional vehicle was added to the mortar in small portions and the product poured into a 1000 mL graduated container. The mortar was rinsed repeatedly with additional vehicle and added to the graduated container to make 800 mL. The product was placed in a 1000 mL beaker, covered and mixed for at least 30 minutes until uniform using a magnetic stirrer.

Six 120-mL amber clear plastic (polyethylene terephthalate) prescription ovals were filled. These containers were fitted with caps lined with low-density polyethylene foam. Three bottles were stored at 5°C and three bottles at 25°C in the absence of light. An initial 5 mL sample was removed from the bulk product and samples were removed from each individual bottle after 1, 2, 7, 10, 14, 28, 35 and 60 days. Prior to sample removal, the bottles were agitated on a rotating mixer for 30 minutes. The pH was determined initially and after 30 and 60 days storage at each temperature. The oral liquids were examined at each sample time for any change in appearance or odor. After the samples were obtained, they were stored at -70°C until analyzed by a validated, stability-indicating high performance liquid chromatographic method.

Table 1: The concentrations of the various drugs used in this study were as follows:

Drug	Concentration (mg/mL)
Acetazolamide	25
Allopurinol	20
Azathioprine	50
Clonazepam	0.1
Flucytosine	10
Ketoconazole	20
Metolazone	1
Metronidazole	50
Procainamide	50
Spironolactone	25



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STABILITY OF EXTEMPORANEOUS FORMULATIONS

Acetazolamide²⁻⁷

Acetazolamide 25 mg/mL Oral Liquid

Rx	Acetazolamide 250 mg Tablets	#12
Vehicle	qs	120 mL

Acetazolamide, a carbonic anhydrase inhibitor, occurs as a white to faintly yellowish-white, odorless, crystalline powder that is very slightly soluble in water and slightly soluble in alcohol. It has pK_a 's of 7.4 and 9.1. The base form is used for oral tablets and the sodium salt for injection. Acetazolamide sodium injection has a pH of 9.2 and is stable for only one week at 2-8° C. The base form should be used for oral liquids to prepare a suspension, which provides for enhanced stability as compared to a solution product.

Acetazolamide retains at least 94% potency in both vehicles at both temperatures studied up to 60 days. This is in agreement with two other studies that projected shelf lives of acetazolamide in oral liquids of 371 days and two years at 25°C. The optimum stability for acetazolamide has been reported to be within the range of pH 4-5.

Table 2: Percent of the initial concentration of acetazolamide (25 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	97.7	101.8	97.5	99.2
14	96.3	100.3	97.8	98.9
28	96.3	101.1	96.9	98.6
60	94.6	100.0	98.6	95.4

The initial pH of the Ora Sweet:Ora Plus mixture was 4.3.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.4.
There was less than 0.5 pH unit change throughout the study.

Allopurinol⁸⁻⁹

Allopurinol 20 mg/mL Oral Liquid

Rx	Allopurinol 300 mg Tablets	#8
Vehicle	qs	120 mL

Allopurinol, a xanthine oxidase inhibitor used in the treatment of gout and some hyperuricemias, is a fluffy white to off-white powder with a slight odor that is very slightly soluble in water and alcohol and has a pK_a of 9.4.

In the current study, allopurinol retains at least 95% potency in both vehicles studied at both temperatures for up to 60 days. This is in agreement with other published work where 97% potency was retained after 56 days storage at both room and refrigerated temperatures, as well as other published data of a stability of at least 14 days when stored in amber glass at 5° C when prepared from crushed tablets in a 1:2 mixture of Cologel:(simple syrup:wild cherry syrup 2:1).

Table 3: Percent of the initial concentration of allopurinol (20 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	98.9	97.6	99.3	99.2
14	97.1	95.2	96.8	95.6
28	98.5	99.7	98.7	96.0
60	95.9	97.6	98.3	96.2

The initial pH of the Ora Sweet:Ora Plus mixture was 4.3.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.3.
There was less than 0.5 pH unit change throughout the study.

Azathioprine^{8,10}

Azathioprine 50 mg/mL Oral Liquid

Rx	Azathioprine 50 mg Tablets	#120
Vehicle	qs	120 mL

Azathioprine is a purine antagonist antimetabolite used mainly for its immunosuppressive activity. It occurs as a pale yellow, odorless powder that is insoluble in water and very slightly soluble in alcohol. It is available as a sodium salt for injection that, when constituted as directed, the solution has a pH of about 9.6. The free form should be used for oral liquids and it is stable in solution at neutral or acid pH but is hydrolyzed to mercaptopurine at alkaline pH.

Azathioprine retained at least 96% potency under the conditions used in this study, as shown below, which is in agreement with previous data presenting 97% and 99.6% potency after storage for 56 days at 25° and 5°C, respectively and another study showing stability of up to 84 days.

Table 4: Percent of the initial concentration of azathioprine (50 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	99.6	99.7	99.2	102.6
14	99.4	98.9	98.8	98.6
28	98.7	97.4	97.8	98.7
60	98.6	96.6	98.1	98.2

The initial pH of the Ora Sweet:Ora Plus mixture was 4.3.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.2.
There was less than 0.5 pH unit change throughout the study.

Clonazepam¹¹

Clonazepam 0.1 mg/mL Oral Liquid

Rx	Clonazepam 2 mg Tablets	#6
Vehicle	qs	120 mL

Clonazepam is a benzodiazepine-derivative anticonvulsant related to diazepam. It occurs as an off-white to light yellow, crystalline powder with a faint odor that is insoluble in water and slightly soluble in alcohol. It has pK_a 's of 1.5 and 10.5.

Clonazepam retained at least 95% activity in the vehicles at the storage conditions listed in this study.

Table 5: Percent of the initial concentration of clonazepam (0.1 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	99.5	99.4	101.4	99.1
14	98.8	97.2	97.8	97.7
28	98.6	95.2	98.3	98.1
60	98.1	95.5	95.6	96.4

The initial pH of the Ora Sweet:Ora Plus mixture was 4.1.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.2.
There was less than 0.5 pH unit change throughout the study.

Flucytosine¹²⁻¹⁴

Flucytosine 10 mg/mL Oral Liquid

Rx Flucytosine 250 mg Capsules #4
Vehicle qs 100 mL

Flucytosine is a non-antibiotic antifungal agent that occurs as a white to off-white, crystalline powder that is odorless and is sparingly soluble in water and slightly soluble in alcohol. It has pK_as of 2.9 and 10.71.

Flucytosine maintained at least 97% potency in the vehicles utilized in this study, which agrees with published data in other vehicles for 60 days at room temperature.

Table 6: Percent of the initial concentration of flucytosine (10 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	99.6	101.1	99.8	100.4
14	98.2	99.0	98.5	98.3
28	99.1	98.8	98.3	98.5
60	98.6	98.0	98.2	97.7

The initial pH of the Ora Sweet:Ora Plus mixture was 4.3.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.4.
There was less than 0.5 pH unit change throughout the study.

Ketoconazole¹⁵

Ketoconazole 20 mg/mL Oral Liquid

Rx Ketoconazole 200 mg Tablets #12
Vehicle qs 120 mL

Ketoconazole is a synthetic imidazole-derivative antifungal agent that occurs as a white to slightly beige powder that is practically insoluble in water and has pK_as of 2.9 and 6.5.

Ketoconazole retained at least 94% potency in these two vehicles. Ketoconazole in a water-based cream is commercially available, with a long shelf-life, so its stability in these vehicles is predictable.

Table 7: Percent of the initial concentration of ketoconazole (20 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	99.5	99.8	99.0	99.1
14	98.1	99.7	98.6	96.5
28	97.4	97.6	97.3	97.1
60	96.2	94.4	97.9	95.9

The initial pH of the Ora Sweet:Ora Plus mixture was 4.5.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.4.
There was less than 0.5 pH unit change throughout the study.

Metolazone¹⁶

Metolazone 1 mg/mL Oral Liquid

Rx Metolazone 10 mg Tablets #12
Vehicle qs 120 mL

Metolazone is a quinazoline-derivative diuretic that occurs as a white powder that is practically insoluble in water and sparingly soluble in alcohol, with a pK_a of 9.7.

Metolazone retained 96% potency for 60 days in both vehicles used in this study at both temperatures.

Table 8: Percent of the initial concentration of metolazone (1 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	99.4	102.1	100.4	100.7
14	101.1	99.6	97.6	99.3
28	101.0	98.7	99.3	99.1
60	100.9	100.0	96.8	100.3

The initial pH of the Ora Sweet:Ora Plus mixture was 4.2.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.1.
There was less than 0.5 pH unit change throughout the study.

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Metronidazole¹⁷⁻¹⁹

Metronidazole 50mg/mL Oral Liquid

Rx Metronidazole Powder 6 g
Vehicle qs 120 mL

Metronidazole is a synthetic, nitroimidazole-derivative antibacterial and antiprotozoal agent that is commercially available as the base and the hydrochloride salt. The base occurs as white to pale yellow crystals or crystalline powder that is sparingly soluble in water and in alcohol, with a pKa of 2.6. Metronidazole hydrochloride occurs as an off-white, lyophilized powder that is very soluble in water and soluble in alcohol; it is used for the injection form. The base, metronidazole, is very stable in solution but the metronidazole hydrochloride in solution is not as stable. Therefore, the metronidazole base should be used for better stability of extemporaneously prepared oral liquids.

Metronidazole retained at least 96% potency in both vehicles studied. It is reported to be stable for 60 days in products with an acidic pH. Commercially available intravenous aqueous solution has an expiration period of 24 months at a pH of 4.5 to 7.0, which also supports this current data. One study of metronidazole 15 mg/mL revealed stability for at least 6 months at 5°C.

Table 9: Percent of the initial concentration of metronidazole (50 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	98.7	99.6	101.3	99.6
14	98.1	97.9	98.1	98.7
28	97.8	96.6	99.5	100.5
60	100.1	96.1	99.0	99.1

The initial pH of the Ora Sweet:Ora Plus mixture was 4.2. The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.3. There was less than 0.5 pH unit change throughout the study.

Procainamide Hydrochloride²⁰⁻²²

Procainamide Hydrochloride 50 mg/mL Oral Liquid

Rx Procainamide Hydrochloride 250 mg Capsules #24
Vehicle qs 120 mL

Procainamide hydrochloride is an antiarrhythmic agent that occurs as a white to tan, hygroscopic, crystalline powder and is very soluble in water and soluble in alcohol; with a pKa of 9.23.

Procainamide retained at least 93% potency over 60 days. A published study found at least six months stability at 5°C in concentrations of 5 and 50 mg/mL of procainamide in extemporaneously compounded oral liquids. Another study projected a shelf-life of 97 days at 25°C.

Table 10: Percent of the initial concentration of procainamide hydrochloride (50 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.

Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	98.7	99.4	102.1	98.6
14	98.1	97.5	97.6	97.8
28	97.9	95.9	98.1	94.8
60	96.4	95.1	96.5	93.4

The initial pH of the Ora Sweet:Ora Plus mixture was 4.4. The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.5. There was less than 0.5 pH unit change throughout the study.

Spirolactone²³⁻²⁶

Spirolactone 25 mg/mL Oral Liquid

Rx Spirolactone 25 mg Tablets #120
Vehicle qs 120 mL

Spirolactone is a synthetic steroid aldosterone antagonist that occurs as a light cream-colored to light tan, crystalline powder with a faint to mild mercaptan-like odor. It is practically insoluble in water and soluble in alcohol.

Spirolactone retained 97% potency in both vehicles for the 60 days. One study projected a two year expiration date at room temperature, utilizing other vehicles. Another study of spiro lactone tablets in cherry syrup showed the product was stable for a minimum of 30 days. An oral suspension of the drug prepared from commercially available tablets has been reported to be stable for one month when prepared with cherry syrup and stored at 5°C.

Table 11: Percent of the initial concentration of spiro lactone (25 mg/mL) remaining after packaging in plastic prescription containers and storage at 5°C or 25°C for up to 60 days.




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Time (Days)	Ora-Sweet:Ora Plus		Ora-Sweet SF:Ora Plus	
	5°	25°	5°	25°
1	96.5	97.5	99.6	98.1
14	98.7	98.6	99.4	100.1
28	97.7	97.4	100.2	96.2
60	97.6	97.6	99.4	99.6

The initial pH of the Ora Sweet:Ora Plus mixture was 4.4.
The initial pH of the Ora Sweet SF:Ora Plus mixture was 4.2.
There was less than 0.5 pH unit change throughout the study.

SUMMARY

In summary, it appears that acetazolamide, allopurinol, azathioprine, clonazepam, flucytosine, ketoconazole, metolazone, metronidazole, procainamide and spironolactone can be mixed with Ora-Sweet:Ora-Plus (1:1) or Ora-Sweet SF:Ora-Plus (1:1) and used over a 60 day period and still retain at least 90% of the original concentration. Pharmacists should be able to compound formulations extemporaneously at the concentrations presented here in 1:1 mixtures of Ora-Sweet:Ora Plus or Ora-Sweet SF:Ora Plus and be assured of physical and chemical stability of at least 60 days, when packaged in light-resistant containers of the materials used in this study.

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