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

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INTRODUCTION

A large number of drugs are prepared extemporaneously by pharmacists as oral liquid dosage forms. Extemporaneous compounding of this type usually involves preparing an oral liquid from a commercially available dosage form (tablets, capsules, injections) or from the pure drug powder.

Ora-Plus™, Ora-Sweet™ and Ora-Sweet SF™ are vehicles that are compatible with many drugs. It is important that the drug be stable in the vehicle for the proposed duration of storage and administration of the product. Each vehicle possesses unique physicochemical characteristics that determine its suitability for use with various drugs. These characteristics include pH, viscosity, taste, appearance, presence of preservatives, and stability. The vehicle selected must be compatible with the drug and the drug must be stable in the vehicle for the proposed duration of storage and administration of the product.

The purpose of this study was to determine the physical and chemical stability of extemporaneous oral formulations of alprazolam, bethanechol chloride, chloroquine phosphate, cisapride, enalapril maleate, hydralazine hydrochloride, pyrazinamide, quinidine sulfate, rifampin and tetracycline hydrochloride,drugs commonly prescribed in oral liquid dosage forms. This stability data enables pharmacists to make informed professional decisions about vehicle selection and the assignment of expiration periods.

STABILITY STUDY DESIGN

Drug selection for this study was based on the results of an informal survey mailed to community and hospital pharmacies. The products and the concentrations selected for this study are shown in Table 1; they were prepared in Ora-Sweet:Ora-Plus (1:1) and Ora-Sweet SF:Ora-Plus (1:1). The sources of the drugs were commercially available dosage forms.

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The Ora-Sweet and Ora-Plus products are of defined composition from lot to lot, which is an advantage for the compounding pharmacist in assessing chemical and physical stability of various additives.

Table 1: Initial concentration of the active drugs used in the study.

Drug	Concentration(mg / mL)
Alprazolam	1
Bethanechol	5
Chloroquine Phosphate	15
Cisapride	1
Enalapril Maleate	1
Hydralazine Hydrochloride	4
Pyrazinamide	10
Quinidine Sulfate	10
Rifampin	25
Tetracycline Hydrochloride	25

Capsules were emptied into a mortar and the powder broken up with a pestle. Tablets were thoroughly comminuted in a mortar with a pestle to obtain a fine powder. A portion of the vehicle was added and mixed with the powder to form a uniform paste. Additional aliquots of the vehicle were added with mixing until the final volume was obtained. Sufficient product was prepared so that triplicate samples for each vehicle could be placed in plastic containers and stored at two different temperatures. The product was filled in three separate 120 mL amber plastic (polyethylene terephthalate, PETG) "prescription ovals" with low density polyethylene foam cap linings and stored at 5° and 25° C, in the absence of light. Samples (5 mL) were removed initially and after 1, 2, 7, 10, 14, 28, 35 and 60 days. The containers were agitated on a rotating mixer for 30 minutes prior to obtaining the sample. The apparent pH was determined initially and after 30 and 60 days of storage. The oral liquids were examined at each sampling time for any change in appearance or odor.

The samples were analyzed using validated, stability-indicating assays. Stability was defined as the retention of not less than 90% of the original concentration of the active drug.

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STABILITY OF EXTEMPORANEOUS FORMULATIONS

Alprazolam

Alprazolam 1 mg/mL

Rx	Alprazolam	2 mg Tablets	#60
	Vehicle	qs	120 mL

Alprazolam 1 mg/mL retained at least 91% of the initial drug concentration in both vehicles studied at both room and refrigerated temperatures for up to 60 days. Alprazolam is a white to off-white, crystalline powder that is insoluble in water and soluble in alcohol.[1] The stability of alprazolam may be enhanced by its poor aqueous solubility and its presence in these liquid vehicles in a suspension dosage form.

Table 2: Percent of the initial concentration of alprazolam (1 mg/mL) remaining after packaging in plastic prescription containers and storage at 5˚C or 25˚C for up to 60 days.

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	99.3	99.0	99.7	99.9
14	99.0	93.9	98.9	98.8
28	97.8	93.6	98.6	98.2
60	96.6	95.4	97.7	96.4

The initial pH of the Ora-Sweet:Ora-Plus mixture was 4.7.
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.

Bethanechol

Bethanechol Chloride 5 mg/mL

Rx	Bethanechol	Chloride 50 mg Tablets	#12
	Vehicle	qs	120 mL

Bethanechol chloride retains at least 92% of the original concentration in Ora-Sweet:Ora-Plus at both temperatures for 60 days, and at least 93% of the original concentration in Ora-Sweet SF:Ora-Plus at both temperatures for 60 days. These results are similar to those obtained by Gupta and Maswoswe[2] who demonstrated almost 100% potency of bethanechol chloride in solution (1 mg/mL) in vehicles such as simple syrup, water, buffer solutions (pH 3.0 to 6.8) over 40 days storage at 25˚C. Schlatter and Saulnier[3], however, showed products (1 mg/mL) in water for irrigation were stable for 40 days when stored at 4˚C at pH of 6.5, but not stable after that; also, solutions prepared from sterile water for injection were stable for only 21 days. No reason was given in their study to the observation that the solution prepared from sterile water for injection (pH 5.4) was not as stable as that prepared from sterile water for irrigation (pH 6.5). An expiration period of 60 days for tablets in preserved water, at a concentration of 0.4 mg/mL and stored in a refrigerator has also been reported by another reference[4].

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

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	98.9	99.0	99.4	98.8
14	96.3	93.5	94.0	94.4
28	96.2	92.4	93.0	93.2
60	95.4	92.1	94.3	93.5

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 4.4.
There was less than 0.5 pH unit change throughout the study.

Chloroquine Phosphate

Chloroquine Phosphate 15 mg/mL

Rx	Chloroquine Phosphate 500 mg Tablets	#3
	Vehicle qs	100 mL

Chloroquine phosphate 15 mg/mL retained at least 98% of the initial drug concentration in these vehicles studied at both room and refrigerated temperatures for up to 60 days. These results are in agreement with a study by Odusote and Nasipuri[5] showing the stability of chloroquine in three syrup formulations over 12 weeks. Their study used either sucrose syrups or methylcellulose solutions adjusted to a pH of 4.5 to 4.9, along with preservatives, coloring and other excipients. Another report mentions stability for at least 30 days for a 25 mg/mL suspension at a pH of 4-6 for 30 days.[6] Also, 20 mg/mL chloroquine in simple syrup was shown to be physically stable after storage at 49˚C for 63 hours and at -6˚C for 8 hours and returned to room temperature.[7] Chloroquine is more stable when protected from light.[8] Chloroquine phosphate is a white, odorless, crystalline powder with a bitter taste that exists in two polymorphic forms. Since it is freely soluble in water, the chloroquine phosphate preparations here were solutions of the active drug.[9] The pH of a 1% solution of the drug is 4.5.[10]

Table 4: Percent of the initial concentration of chloroquine phosphate (15 mg/mL) remaining after packaging in plastic prescription containers and storage at 5˚C or 25˚C for up to 60 days.

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	99.5	99.9	99.5	99.8
14	99.1	99.5	99.5	99.0
28	97.9	99.3	99.2	98.8
60	98.1	99.0	99.3	98.8

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.

Cisapride

Cisapride 1 mg/mL

Rx	Cisapride 10 mg Tablets	#12
	Vehicle qs	120 mL

Note: Adjust the pH of the final product to about 7.0 using sodium bicarbonate.

Cisapride 1 mg/mL retained at least 91% of the initial drug concentration in both vehicles studied at both room and refrigerated temperatures for up to 60 days, when adjusted to a pH of 7.

Cisapride has been demonstrated by Nahata et al to be stable for at least 91 days of storage at refrigerated temperature and 28 days at room temperature. Their study used products formulated with a vehicle of methylcellulose 1% and simple syrup.[11] Horn and Anderson[12] studied a formulation consisting of cherry syrup and propylene glycol with the pH adjusted to greater than 6.5 with sodium bicarbonate which showed stability at room temperature for at least 3 weeks. It is important to adjust the pH to neutral to enhance stability of this product.

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

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	99.5	99.8	99.2	99.0
14	98.2	97.4	96.3	95.7
28	99.6	96.8	95.9	94.9
60	97.9	93.8	94.2	92.9

The initial pH of the Ora-Sweet:Ora-Plus mixture was **7.0**.
The initial pH of the Ora-Sweet SF:Ora-Plus mixture was **7.0**.
There was less than 0.5 pH unit change throughout the study.

Enalapril Maleate

Enalapril Maleate 1 mg/mL

Rx	Enalapril Maleate 20 mg Tablets	#6
	Vehicle qs	120 mL

Enalapril maleate 1 mg/mL retained at least 94% of the initial drug concentration in both vehicles studied at both room and refrigerated temperatures for up to 60 days. Enalapril maleate is a white to off-white crystalline powder that is soluble in water to the extent of 25 mg/mL and in alcohol at 80 mg/mL.[13] It has pK_as of 3 and 5.4 and a reported pH of maximum stability of about 3.[14] Above pH 5, an increased rate of decomposition occurs. At room temperature, one report provides t_{90} results for 0.5 mg/mL solutions at pH 2 and 5 of 262 and 114 days, respectively.[15] Another study reports on the use of enalapril maleate tablets to prepare an oral liquid in 0.1 and 1.0 mg/mL concentrations in an isotonic citrate buffer at pH 5.[16] The products were stable at 5˚C for 90 days but at 25˚C the 0.1 and 1.0 mg/mL preparations were stable for only 55 and 43 days, respectively. One should note, however, that the buffered pH of 5 was above that of maximum stability. The preparations of Ora-Plus in this current study had pH values in the range of 3.92 to 4.77, somewhat closer to that of maximum stability.

Table 6: Percent of the initial concentration of enalapril maleate (1mg/mL) remaining after packaging in plastic prescription containers and storage at 5˚C or 25˚C for up to 60 days.

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	98.7	99.5	99.9	99.8
14	98.2	98.9	98.7	98.1
28	97.8	98.0	98.1	97.5
60	95.6	94.4	97.7	96.9

The initial pH of the Ora-Sweet:Ora-Plus mixture was 4.8.
The initial pH of the Ora-Sweet SF:Ora-Plus mixture was 4.7.
There was less than 0.5 pH unit change throughout the study.

Hydralazine Hydrochloride

Hydralazine Hydrochloride 4 mg/mL

Rx	Hydralazine Hydrochloride 100 mg Tablets	#4
	Vehicle qs	100 mL

Hydralazine hydrochloride 4 mg/mL was not very stable in any of these vehicles. In the Ora-Sweet:Ora-Plus, it was only stable for 1 day at 5˚C and in Ora-Sweet SF:Ora-Plus it was stable for about 5 days (interpolated value) at 5˚C. The product was not stable for even a day at 25˚C in the Ora-Sweet:Ora-Plus vehicles. Hydralazine hydrochloride is a white to off-white/yellow, crystalline powder that is soluble to the extent of 40 mg/mL in water and 2 mg/mL in alcohol. It has a pKa of 7.3 and the commercially available injection has a pH in the range of 3.4 to 4.17. The pH of a 2% aqueous solution is in the range of 3.5 to 4.5.[18] Numerous studies have been reported on the stability of extemporaneously compounded hydralazine hydrochloride products using various vehicles. Alexander reported on a formulation consisting of 1.25 mg/mL hydralazine hydrochloride in maltitol, edetate sodium, sodium saccharin, methylparaben, propylparaben, propylene glycol, orange flavoring and water, using acetic acid to adjust the pH to 3.7.[19] The product was relatively stable with less than 2% loss of drug at 5˚C in two weeks and a calculated shelf life at 25˚C from accelerated temperature data of about 5.13 days. The same authors found hydralazine hydrochloride to be incompatible with edetate sodium and sodium bisulfite in aqueous solution.

Gupta reported the stability of 1% hydralazine hydrochloride in aqueous vehicles containing various sugars, including dextrose, fructose, lactose and maltose, and showed these sugars to have deleterious effects on the stability of the drug with losses of 30-70% occuring in 24 hours for samples stored

in amber bottles at 24˚C.[20] When the drug was mixed in vehicles containing hydrolyzed sucrose in simple syrup or strawberry syrup, losses of 93-95% of the active drug occurred in one day. Unhydrolyzed 85% sucrose solutions provided a better vehicle with 1% hydralazine hydrochloride where losses of about 10% occurred at 24˚C in seven days. Sorbitol solutions provided better stability with only 4 and 8% loss in 21 days at 24˚C. The best stability was found using 0.28 M mannitol, with no drug loss occurring after 21 days at 24˚C. The hydralazine hydrochloride oral liquids in this study were prepared from the commercial tablets, containing lactose. Lactose, a reducing sugar, can form an osazone, increasing the degradation rate of the hydralazine.[21]

For hydralazine, it may be more appropriate to only prepare sufficient product for 24 hours at a time for the patient. Another alternative would be to dispense it in such a manner that it can be mixed immediately prior to administration, i.e., pulverizing the commercial tablets and pre-filling single doses in individual capsules. The caregiver could be counseled to empty the contents of a single capsule into one teaspoonful of vehicle for administration. Although not ideal, it may enhance positive patient outcomes.

Table 7: Percent of the initial concentration of hydralazine hydrochloride (4 mg/mL) remaining after packaging in plastic prescription containers and storage at 5˚C or 25˚C for up to 60 days.

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	91.3	78.3	97.3	87.0
14	51.1	28.1	78.1	39.3
28	38.3	23.9	65.8	32.9
60	19.6	17.3	48.5	25.2

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 4.3.
There was less than 0.5 pH unit change throughout the study.

Pyrazinamide

Pyrazinamide 10 mg/mL

Rx	Pyrazinamide 500 mg Tablets		#3
	Vehicle	qs	150 mL

Pyrazinamide retains at least 97% of the original concentration in Ora-Sweet:Ora-Plus and 98% in Ora-Sweet SF:Ora-Plus at both temperatures for 60 days. The current results for pyrazinamide are supported by a study in different vehicles by Nahata, Morosco and Peritore[22]. These investigators reported on the stability of pyrazinamide 100 mg/mL in two vehicles: one containing simple syrup and the second containing methylcellulose and simple syrup. They found that pyrazinamide in both suspensions exceeded 90% of their initial concentration throughout the two-month study period at both refrigerated and room temperatures. A study by Seifart, Parkin and Donald[23], however, in a vehicle of tragacanth, concentrated chloroform water and water showed stability at 4˚C for 22 days, 24˚C for 19 days and at 40˚C for only 8 days.

Table 8: Percent of the initial concentration of pyrazinamide (10 mg/mL) remaining after packaging in plastic prescription containers and storage at 5˚C or 25˚C for up to 60 days.

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	99.8	99.5	99.7	99.5
14	98.3	98.1	98.9	98.5
28	97.5	98.4	98.8	98.6
60	97.3	97.9	98.8	98.4

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.

Quinidine Sulfate

Quinidine Sulfate 10 mg/mL

Rx	Quinidine Sulfate 200 mg Tablets		#6
	Vehicle	qs	120 mL

Quinidine sulfate retained at least 97% of the original potency in Ora-Sweet:Ora-Plus and 96% in Ora-Sweet SF:Ora-Plus vehicles at both temperatures over the 60 day study period.

The stability of quinidine sulfate has been reported as 30 days at refrigerated temperatures in two vehicles, one consisting of simple syrup and the other consisting of 10-12.5% ethanol in citric acid syrup.[24]

Table 9: Percent of the initial concentration of quinidine sulfate (10 mg/mL) remaining after packaging in plastic prescription containers and storage at 5˚C or 25˚C for up to 60 days.

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	101.1	100.7	100.9	100.1
14	98.8	100.4	98.7	99.5
28	99.3	99.1	99.0	99.1

60	98.1	97.4	96.3	98.5

The initial pH of the Ora-Sweet:Ora-Plus mixture was 3.9.
The initial pH of the Ora-Sweet SF:Ora-Plus mixture was 3.9.
There was less than 0.5 pH unit change throughout the study.

Rifampin

Rifampin 25 mg/mL

Rx	Rifampin 300 mg Capsules	#10
	Vehicle qs	120 mL

Rifampin retained potencies for only **28** days at both temperatures of at least 91% in Ora-Sweet:Ora-Plus and 90% in Ora-Sweet SF:Ora-Plus. The 28 day stability of rifampin in the vehicles in this study are similar to other studies. Allen[25] reported on 1% rifampin suspensions prepared using either simple syrup, wild cherry syrup or Syrpalta™ where a 4 week stability at refrigeration temperatures was suggested. Krukenberg et al[26] also recommended a 4 week period in their study of 1% rifampin suspensions formulated using syrup NF, simple syrup (Humco), simple syrup (Whiteworth), wild cherry syrup and Syrpalta and storage at both room and refrigerated temperatures. Nahata[27] reported that the preparation method can influence the dispersion of the drug in the vehicle. There was a difference depending upon whether the product was prepared from the capsules or the parenteral solution. He reported a stability of 56 days in syrup for products stored in the refrigerator.

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

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	98.5	99.1	99.8	99.5
14	93.0	96.5	93.9	92.4
28	91.1	92.4	91.5	90.8
60	86.1	85.1	88.1	86.4

The initial pH of the Ora-Sweet:Ora-Plus mixture was 4.8.
The initial pH of the Ora-Sweet SF:Or--Plus mixture was 4.6.
There was less than 0.5 pH unit change throughout the study.

Tetracycline Hydrochloride

Tetracycline Hydrochloride 25 mg/mL

Rx	Tetracycline Hydrochloride 500 mg Capsules	#6
	Vehicle qs	120 mL

Tetracycline hydrochloride retained at least 90% of the initial concentration in Ora-Sweet:Ora-Plus at both temperatures for 28 days and in Ora-Sweet SF:Ora-Plus at 5˚C for 10 days, 25˚C for 7 days. It should be recommended that the oral liquid tetracycline preparation be prepared from the tetracycline base powder. The problem may be one of solubility. For example, tetracycline hydrochloride has an aqueous solubility of about 100 mg/mL.[28] If tetracycline base is used, its solubility in water is only about 0.4 mg/mL. At a concentration of 25 mg/mL in the vehicles used in this study, the tetracycline hydrochloride was in solution. If the base was used, the product would be a suspension, with greater stability and a longer stability period. The hydrochloride salt was used in this study because the tetracycline hydrochloride capsules are the most easily available form of the drug and the information was needed.

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

Time	Ora-Sweet:Ora-Plus (1:1)		Ora-Sweet SF:Ora-Plus (1:1)	
(Days)	5˚C	25˚C	5˚C	25˚C
1	99.9	102.6	97.8	96.9
7	98.6	97.9	93.1	90.8
28	92.3	90.9	86.4	81.9
60	88.5	86.4	80.1	74.4

The initial pH of the Ora-Sweet:Ora-Plus mixture was 2.6.
The initial pH of the Ora-Sweet SF:Ora-Plus mixture was 2.7.
There was less than 0.5 pH unit change throughout the study.

SUMMARY

Physical observations, including visual and olfactory observations, did not reveal any substantial changes during the storage time for any of the formulations.

Alprazolam 1 mg/mL, bethanechol chloride 5 mg/mL, chloroquine phosphate 15 mg/mL, cisapride 1 mg/mL. enalapril maleate 1 mg/mL, pyrazinamide 10 mg/mL and quinidine sulfate 10 mg/mL can be compounded extemporaneously from capsules or tablets using Ora-Sweet:Ora-Plus (1:1) and Ora-Sweet:Ora-Plus SF (1:1) vehicles and are stable for 60 days when stored in the absence of light at both 5˚ and 25˚C.

Hydralazine hydrochloride 4 mg/mL was only stable at 5˚ C for one day in Ora-Sweet:Ora-Plus and two days in Ora-Sweet SF:Ora-Plus. Rifampin 25 mg/mL extemporaneously prepared in these vehicles can be stored for up to 28 days at both storage temperatures. Tetracycline hydrochloride 25 mg/mL, however, was

only stable in Ora-Sweet:Ora-Plus for 28 days at both temperatures; in Ora-Sweet SF:Ora-Plus for 10 days in the refrigerator and 7 days at room temperature; and in cherry syrup, for only 7 days in the refrigerator and 2 days at room temperature. **It is recommended that the tetracycline base powder be used when preparing tetracycline oral liquid.**

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