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Stability Of Extemporaneously Prepared Oral Liquid Formulations – Part X

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. Explain the difference between potency and stability-indicating assay methods.
2. Determine the "beyond-use date" of each of the ten preparations discussed.
3. Determine the appropriate storage temperature to ensure the stability of the preparations.
4. Discuss the methods of preparation of selected drugs using modified release dosage forms.

INTRODUCTION

Potency vs Stability Testing

Potency tests are designed to determine how much of an active drug is in a sample. Stability tests are used to determine an expiration date of a product or a beyond-use date of a preparation. Being able to employ the proper method to determine potency or stability is the key to understanding the difference between potency testing versus stability testing. In order to determine potency, a method may or may not be stability-indicating. When determining stability, the method must be stability-indicating. When using a stability-indicating method, both potency and stability can be determined. Quality assurance programs are essential to establishing standards for compounded preparations. It is important that compounding pharmacists understand the differences between potency and stability tests and that these tests are made an integral part of the quality assurance program.

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)
Ciprofloxacin hydrochloride	50
Diclofenac sodium	10
Famotidine	8
Gabapentin	100
Itraconazole	20
Mycophenolate mofetil	100
Ondansetron hydrochloride	0.8
Oxandrolone	1
Thalidomide	20
Venlafaxine hydrochloride	15

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STABILITY OF EXTEMPORANEOUS FORMULATIONS

Ciprofloxacin hydrochloride

($C_{17}H_{18}FN_3O_3.HCl.H_2O$, MW 385.82) occurs as faintly yellowish to light yellow crystals. It is sparingly soluble in water and very slightly soluble in dehydrated alcohol. Ciprofloxacin hydrochloride 50 mg/mL was prepared by gradually adding equal amounts of ORA-Plus and Simple Syrup NF to the contents of crushed 750 mg ciprofloxacin hydrochloride tablets in a glass mortar to final volume. Six identical suspensions were prepared and packaged in plastic, two-ounce amber prescription bottles with child-resistant caps; three were stored at room temperature and three under refrigeration. The samples were analyzed for content, color, taste, odor and pH; microbiological testing was not performed. Results showed no detectable change in color or odor and no visible microbiological grown in any sample. There was no appreciable change in pH (4.48 +/- 0.1) in any of the samples. The results in Table 2 show that the preparations were stable for at least 56 days in amber, plastic prescription bottles at room or refrigerated temperature.[1,2]

Table 2: Stability of ciprofloxacin hcl 50 mg/mL in a 1:1 mixture of ORA-Plus and Syrup NF stored at both room and refrigerated temperatures.

Storage Temp	% of Initial Concentration Remaining				
	Day 0	Day 7	Day 14	Day 28	Day 56
23-25° C	51.6 (1.3)[a]	100.0 (3.0)	99.8 (1.0)	100.4 (3.4)	100.5 (3.5)
3-5° C	50.9 (2.0)[a]	99.9 (2.6)	99.8 (3.0)	99.4 (3.4)	99.6 (2.8)

[a] Mean (±S.D.) initial concentration (mg/mL)

Diclofenac sodium

($C_{14}H_{10}C_{12}NNaO_2$, MW 318.13) occurs as a white to off-white, hygroscopic crystalline powder. It melts about 284° C and is sparingly soluble in water. Diclofenac sodium 10 mg/mL was prepared from commercially available diclofenac sodium enteric coated tablets. The tablets were ground to a powder and then combined with ORA-Blend to create a 10 mg/mL suspension. The suspension was placed in 60 mL amber PVC prescription bottles and stored at either 5° C or at 23° C for 93 days; all bottles were protected from light. The pH of the suspensions did not change more than 0.07 units during storage and remained at about pH 6.0 (6.04 to 6.11) for the duration of the study. All suspensions were deemed stable for at least 93 days using both storage conditions, as shown in Table 3.[1,3]

Table 3: Stability of diclofenac sodium 10 mg/mL suspension in ORA-Blend.

Storage Temp	% of Initial Concentration Remaining				
	Day 0	Day 14	Day 27	Day 56	Day 93
23-25° C	9.0 (0.28)[a]	101.2 (1.1)	102.6 (0.9)	100.6 (1.2)	101.2 (0.9)
3-5° C	8.9 (0.13)[a]	99.5 (1.4)	99.8 (1.8)	105.4 (1.7)	99.8 (1.1)

[a] Mean (±S.D.) initial concentration (mg/mL)

Famotidine

($C_8H_{15}N_7O_2S_3$, MW 337.43) occurs as a white to pale yellowish-white, crystalline powder. It is sensitive to light and very slightly soluble in water. Famotidine 8 mg/mL suspension was prepared using famotidine tablets in equal volumes of ORA-Plus and ORA-Sweet. Samples were packaged in 2 ounce amber polyethylene terephthalate bottles with child-resistant caps at room temperature for up to 95 days. The pH of the suspensions was 5.8 initially and remained unchanged throughout the study; there was no detectable change in color or odor and no visible microbial growth in any sample. The suspension retained more than 90% of its initial famotidine concentrations for 95 days at 23-25° C.[1,4]

Gabapentin

($C_9H_{17}NO_2$, MW 171.24) occurs as a white to off-white crystalline solid that is freely soluble in water at both alkaline and acidic pH. Gabapentin 100 mg/mL oral suspensions were prepared using gabapentin capsules. Two vehicles were prepared; one in 1% methylcellulose in syrup (1:1) and another in equal volumes of ORA-Plus:ORA-Sweet. The suspensions were stored in two ounce plastic prescription bottles and stored at either 4 or 25° C for up to 91 days after preparation. Results, as shown in Table 4, demonstrated that gabapentin 100 mg/mL was stable in ORA-Plus and ORA-Sweet 1:1 for at least 56 days at 25° C and 91 days at 4° C. There were no substantial changes in pH, physical appearance, or odor during the 91 day study period.[1,5]

Table 4: Stability of gabapentin 100 mg/mL in ORA-Plus:ORA-Sweet.

Storage Temp	% of Initial Concentration Remaining				
	Day 0	Day 14	Day 28	Day 56	Day 91
23-25° C	102.21 (1.93)[a]	99.03 (1.89)	97.17 (2.03)	93.81 (3.19)	91.32 (3.37)
3-5° C	102.96 (1.67)[a]	99.93 (1.98)	98.07 (2.07)	97.04 (2.11)	95.02 (2.73)

[a] Mean (±S.D.) initial concentration (mg/mL)
pH 5.58 (0.005) room temperature; pH 5.48 (0.008) refrigerated temperature

Itraconazole

($C_{35}H_{38}C_{12}N_8O_4$, MW 705.63) occurs as a white or almost white powder that is practically insoluble in water. Itraconazole 20 mg/mL suspension was prepared from the capsules in a 1:1 mixture of ORA-Sweet and ORA-Plus. The suspension was packaged in two ounce amber plastic prescription bottles and stored at either 25° or 4° C and sampled for up to 91 days. Results showed no appreciable changes in color, odor or pH (5.23). Itraconazole was stable for up to 56 days at both storage conditions, as shown in Table 5.[1,6]

Table 5: Stability of itraconazole 20 mg/mL in 1:1 ORA-Sweet and ORA-Plus.

Storage Temp	% of Initial Concentration Remaining				
	Day 0	Day 7	Day 28	Day 56	Day 91
23-25° C	16 (0.85)[a]	104.6 (1.5)	95.3 (2.7)	91.9 (1.6)	85.9 (1.5)
3-5° C	15.9 (0.86)[a]	93.7 (4.0)	93.7 (3.7)	95.0 (2.9)	89.8 (2.8)

[a] Mean (±S.D.) initial concentration (mg/mL)

Mycophenolate mofetil

($C_{23}H_{31}NO_7$, MW 433.49) occurs as a white to off-white crystalline powder. It is soluble, 43 µg/mL in water at pH 7.4 and 4.27 mg/mL at pH 3.6. Mycophenolate mofetil 100 mg/mL was prepared using the capsules and a vehicle of ORA-Plus with artificial cherry flavoring, FD&C Red No. 40 and aspartame. At room temperature, the cherry flavor often disappeared on storage leaving a strong musty odor; the authors recommended the preparation be stored at refrigerated temperature to retain the cherry flavor. The pH (5.9) remained unchanged throughout the study. The initial concentration was 96.8 (1.9) mg/mL. After 30 days, the percent remaining was 103.8 (1.5) and after 120 days, was 100.3 (1.7).[1,7]

Ondansetron hydrochloride

($C_{18}H_{19}N_3O.HCl._2H_20$, MW 365.85) occurs as a white to off-white powder that is sparingly soluble in water and in alcohol. Ondansetron hydrochloride 0.8 mg/mL was prepared from the tablets in a 1:1 mixture of either ORA-Plus:ORA-Sweet or ORA-Plus:ORA-Sweet SF. The preparations were packaged in amber plastic vials and stored at 4° C for up to 42 days. Results showed that all the ORA-Plus:ORA-Sweet and ORA-Plus:ORA-Sweet SF preparations remained greater than 90% of the initial concentration throughout the 42 day study period, as shown in Table 6. The pH of these preparations was 4.1.[1,8]

Table 6: Stability of ondansetron hcl 0.8 mg/mL in ORA-Plus:ORA-Sweet or ORA-Plus:ORA-Sweet SF stored at 4° C.

	% of Initial Concentration Remaining				
	Day 0	Day 10	Day 21	Day 35	Day 42
ORA-Plus:ORA-Sweet					
	0.896 (0.026)[a]	102.9 (4.9)	98.1 (6.7)	96.5 (2.9)	101.4 (7.3)
ORA-Plus:ORA-Sweet SF					
	0.808 (0.024)[a]	101.6 (2.2)	100.5 (3.6)	99.5 (2.3)	97.1 (4.9)

[a] Mean (±S.D.) initial concentration (mg/mL)

Oxandrolone

($C_{19}H_{30}O_3$, MW 306.44) occurs as a white, odorless, crystalline powder that is stable in air but darkens on exposure to light. It melts at about 225° C and is sparingly soluble in alcohol and practically insoluble in water. Oxandrolone 1 mg/mL oral suspension was prepared using oxandrolone tablets and 1:1 ORA-Plus: ORA-Sweet or ORA-Plus:ORA-Sweet SF. The preparation was packaged in 2 ounce amber plastic bottles at room temperature and sampled up to 90 days. At least 98% of the original oxandrolone concentration was retained at the end of the 90 day study period as shown in Table 7; there was no appreciable change in odor, taste, color or pH (4.35 and 4.31 for the ORA-Plus:ORA-Sweet and ORA-Plus:ORA-Sweet SF, respectively).[1,9]

Table 7: Stability of oxandrolone in ORA-Plus: ORA-Sweet and ORA-Plus:ORA-Sweet SF stored at 23-25° C.

	% of Initial Concentration Remaining				
	Day 0	Day 7	Day 35	Day 60	Day 90
ORA-Plus:ORA-Sweet					
	1.01 (0.02)[a]	100.18 (1.61)	100.97 (1.43)	100.05 (1.65)	98.17 (1.75)
ORA-Plus:ORA-Sweet SF					
	0.99 (0.02)[a]	100.46 (0.88)	100.44 (1.22)	99.73 (1.62)	98.96 (2.21)

[a] Mean (±S.D.) initial concentration (mg/mL)

Thalidomide

($C_{13}H_{10}N_2O_4$, MW 258.23) occurs as a white to off-white powder that is sparingly soluble in water. Thalidomide 20 mg/mL suspension was prepared using the capsules and ORA-Plus:ORA-Sweet 1:1. The preparation was placed in 2 ounce amber plastic bottles with child-resistant caps and stored in a refrigerator. Samples were withdrawn and analyzed for up to 35 days. At least 92% of the initial concentration was retained throughout the 35 day study period as shown in Table 8 with no detectable changes in color, odor or pH (4.32) and no visible microbial growth in a sample.[1,10]

Table 8: Stability of thalidomide 20 mg/mL in ORA-Plus:ORA-Sweet stored at 4° C.

% of Initial Concentration Remaining				
Day 0	Day 7	Day 14	Day 21	Day 35
20.00 (0.08)[a]	100.03 (0.84)	100.41 (1.38)	99.75 (1.82)	93.38 (0.74)

[a] Mean (±S.D.) initial concentration (mg/mL)

Venlafaxine hydrochloride

($C_{17}H_{27}NO_2$.HCl, MW 313.86) occurs as a white to off-white crystalline powder that is soluble in water. Venlafaxine 15 mg/mL was prepared from extended-release microspheres that were reduced to a powder and suspended in ORA-Plus:ORA-Sweet 1:1. Samples were placed in 120 mL plastic, amber oral liquid bottles and stored at either room or refrigerated temperatures for up to 28 days. As shown in Table 9, there was no loss of venlafaxine over the duration of the study period. There was no change in color and only a slight change in pH from 6.21 to 6.03.[1,11]

Table 9: Stability of venlafaxine hcl 15 mg/mL in ORA-Plus:ORA-Sweet 1:1.

Storage Temp	% of Initial Concentration Remaining				
	Day 0	Day 7	Day 14	Day 21	Day 28
23° C	12.4 (0.46)[a]	97.1 (2.5)	99.6 (2.3)	101.8 (1.1)	99.9 (0.8)
5° C	12.2 (0.22)[a]	101.8 (0.9)	97.9 (2.0)	101.5 (1.4)	100.5 (1.4)

[a] Mean (±S.D.) initial concentration (mg/mL)

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