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Stability Of Extemporaneously Prepared Oral Liquid Formulations – Part XI

Goal: To provide information on the occurrence, causes and prevention of compounding errors.

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

1. List three areas of concern when using commercial products as the drug source.
2. Identify which drugs will be in solution or as a suspension based on their solubility.
3. Identify an accelerated stability study based on the temperature at which it is conducted.
4. Evaluate tabular data and determine the beyond-use date (BUD) of a preparation.

INTRODUCTION

With Part 11 of this series, we have reviewed and summarized 110 drugs in formulations with beyond-use dates established and published in the peer reviewed literature. As there is no national/universal standard for these studies, they sometimes differ in the source of ingredients, methods of preparation, storage containers, temperatures, etc. Generally, it is best to use the pure drug powder as the source of active drug. However, if the pure drug is not available, then a commercially manufactured drug product is used.

The disadvantage to using commercial manufactured drug products as the drug source is:

(1) The manufactured drug product contains excipients that may alter the stability of the drug,

(2) The actual drug content is unknown since variation is permitted, eg 90-110%, of the active drug in the product,

(3) It may make the analytical methods more involved.

Regarding point (2), a pharmacist is limited to assuming the active drug content is 100% of the label. However, many drugs are 95-105%, 90-110%, 80-120%, 90-120% etc. Since the pharmacist does not have access to the analyzed concentration of the drug in the manufactured product, the label quantity of 100% is used but the actual amount present may be less or more. In fact, it may actually result in the compounded preparation being outside the USP allowable of 90-110% for compounded preparations.

Due to the variables just mentioned, it is best to compound the formulation just as it was prepared in the published research stability study. There are some variations allowed and that is up to the pharmacists' professional judgment. Consequently, it is advisable to check the references as applicable.

The extemporaneous preparations presented in this paper include those listed in Table 1 on the following page.

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 receives an honorarium for his contribution to Secundum Artem*

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Table 1: Concentrations of the various drugs in the studies reported in this paper.

Drug	Concentration (mg/mL)
Chlorpromazine HCl	100
Gabapentin	100
Hydrocortisone	0.2
Lamotrigine	1
Levetiracetam	50
Levofloxacin	50
Lorazepam	1
Methotrexate	2
Metronidazole benzoate	16
Perphenazine	0.5

STABILITY OF EXTEMPORANEOUS FORMULATIONS

Chlorpromazine Hydrochloride (C17H19ClN2S.HCl, MW 355.33) occurs as a white or slightly creamy white, odorless, crystalline powder. It darkens on prolonged exposure to light and is very soluble in water. The pH of maximum stability is 6; oxidation of the drug occurs in alkaline media. The drug should be protected from light. A chlorpromazine HCl 100 mg/mL clear solution was prepared in ORA-Sweet® using the powder, packaged in amber plastic prescription ovals and stored at both refrigeration and room temperature conditions. Triplicate samples were obtained after 1, 2, and 3 months of storage. Results, as detailed in Table 2 below, show that the solution is stable at both refrigeration and room temperatures for up to 3 months. The pH of the solutions ranged from 3.50 to 3.77 during the study.

Table 2: Stability of Chlorpromazine HCl 100 mg/mL solution

Storage Temperature (° C)	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining		
		1 month	2 months	3 months
2-8	104.9 +/- 2.0	97.1 (1.8)	101.4 (1.0)	94.2 (0.9)
20-25	104.9 +/- 2.0	97.2 (0.1)	101.4 (1.2)	93.6 (1.6)

Gabapentin (C9H17NO2, MW 171.24) occurs as white to off-white, crystalline solid that is freely soluble in water. Gabapentin 100 mg/mL oral suspension was prepared using a 1:1 mixture of ORA-Plus®/ORA-Sweet® and stored at both room and refrigerated temperatures. The preparation was prepared using Neurontin capsules 300 mg each and stored in amber plastic prescription bottles. As shown in Table 3, the preparation was stable for 91 days at refrigerated and for 56 days at room temperatures. The pH values ranged from pH 5.48 to 5.58.

Table 3: Stability of gabapentin 100mg/mL in two oral suspensions in ORA-Plus®/ORA-Sweet® at 4° C and 25° C.

Storage Temperature (° C)	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining		
		28 days	56 days	91 days
2-8	102.21 (1.93)	98.07 (2.07)	97.04 (2.11)	95.02 (2.73)
20-25	102.96 (1.67)	97.17 (2.03)	93.81 (3.19)	91.32 (3.37)

Hydrocortisone ($C_{21}H_{30}O_5$, MW 362.46) occurs as a white to practically white, odorless, crystalline powder that is very slightly soluble in water. This study involved an accelerated stability study which is conducted at a higher temperature for a shorter time period as compared to a real time study done at routine storage temperatures (room and refrigerated). The data can then be used to estimate the stability at other temperatures. The advantage is the shorter time period required for the study. Hydrocortisone 0.2 mg/mL in ORA-Sweet® was prepared from micronized hydrocortisone powder and stored in clear glass vials for up to 71 days at 60° C in an accelerated stability study; samples were collected and analyzed after 15, 24, 38, and 71 days. The pH of the preparations ranged from 3.6 to 4.1. Results showed that the preparation retained 88.2% (15 days), 82.9% (24 days), 74.6% (38 days) and 67.7% (71 days). Using the Q10 method of estimating stability (derived from the Arrhenius equation) and a conservative estimate at 90%+ of the active drug remaining interpolated to be 10 days (derived from the study) and calculating stability at 20° C (room temperature), the conservative estimate of the stability would be 810 days at room temperature, as follows:

$$t_{90}(T_2) = t_{90}(T_1) / Q_{10}^{(\Delta T/10)}$$

where -$t_{90}(T_2)$ is the stability at the new temperature (20° C)
-$t_{90}(T_1)$ is the stability at the given temperature (est. 10 days at 60° C)
-Q_{10}: using the value of 3
-ΔT is the temperature change (60° to 20° is a -40° change)

$$t_{90}(20) = 10 \text{ days} / 3^{-40/10}$$
$$t_{90}(20) = 10 \text{ days} / 3^{-4}$$
$$t_{90}(20) = 810 \text{ days}$$

So, a BUD of up to 6 months (180 days) stored at room temperature would be a reasonable estimate.

Lamotrigine ($C_9H_7Cl_2N_5$, MW 256.09) occurs as a white to pale cream-colored powder that is slightly soluble in water. Lamotrigine 1 mg/mL in ORA-Plus®/ORA-Sweet® and ORA-Plus®/ORA-Sweet® SF were prepared from commercial tablets, stored in amber polyethylene terephthalate prescription bottles at 4 and 25° C and sampled initially and after 7, 14, 28, 42, 56, 70 and 91 days. Results showed the preparations were stable for at least 91 days as shown in Table 4 below. The pH of the preparations ranged from 4.5 to 4.6.

Table 4: Stability of lamotrigine 1 mg/mL in two oral suspensions in ORA-Plus®/ORA-Sweet® and ORA-Plus®/ORA-Sweet® SF at 4° C and 25° C.

Storage Temperature (° C)	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining			
		14 days	28 days	56 days	91 days
ORA-Plus®/ORA-Sweet®					
4° C	1.02 (0.46)	101.3 (1.1)	100.2 (1.2)	100.9 (1.0)	99.7 (1.7)
25° C	1.03 (0.28)	101.5 (0.6)	100.9 (1.3)	99.4 (1.2)	99.8 (1.6)
ORA-Plus®/ORA-Sweet® SF					
4° C	1.02 (0.39)	100.5 (0.5)	100.0 (1.3)	99.7 (1.8)	99.6 (1.5)
25° C	1.00 (0.37)	101.0 (0.5)	100.2 (0.8)	99.8 (1.5)	99.4 (1.7)

Levetiracetam ($C_8H_{14}N_2O_2$, MW 170.21) occurs as a white to almost white powder that is very soluble in water. Levetiracetam 50 mg/mL was prepared in a 1:1 mixture of ORA-Sweet®/ORA-Plus®, stored in amber plastic prescription bottles, stored at 25° or 4° and sampled on days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84 and 91. Results (Table 5 next page) showed that the preparations were stable for up to 91 days; the pH of the preparations averaged from 4.25 to 4.34.

Table 5: Stability of levetiracetam 50 mg/mL in ORA-Plus®/ORA-Sweet® stored at 4° C and 25° C.

Storage Temperature (° C)	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining 14 days	28 days	56 days	91 days
4	51 (1.5)	100.1 (2.0)	101.8 (4.2)	97.1 (2.4)	94.8 (9.2)
25	50.0 (2.0)	95.3 (2.7)	101.6 (5.3)	100.5 (8.4)	100.0 (6.5)

Levofloxacin (C18H20FN3O4.1/2 H2O, MW 370.38) occurs as a light yellowish-white to yellow-white crystals or crystalline powder that is sparingly soluble in water. Levofloxacin 50 mg/mL was prepared in equal amounts of ORA-Plus® and strawberry syrup. The preparations were stored in amber plastic prescription bottles and stored at either room or refrigerated temperature. They were sampled immediately and after 8, 15, 29 and 57 days of preparation. The results (Table 6) showed that at least 99% of the initial levofloxacin concentration remained in all samples throughout the entire 57 day study period. The pH of the preparations was 6.7 (0.1).

Table 6: Stability of levofloxacin 50 mg/mL in ORA-Plus® with Strawberry syrup and stored at 4° C and 25° C.

Storage Temperature (° C)	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining 8 days	15 days	29 days	57 days
4	50.18 (2.07)	100.24 (1.50)	99.91 (1.97)	100.49 (2.80)	100.10 (3.25)
25	50.01 (1.59)	99.80 (2.63)	100.70 (1.33)	101.01 (3.72)	100.18 (1.28)

Lorazepam (C15H10Cl2N2O2, MW 321.16) occurs as a white or practically white, practically odorless powder that is insoluble in water. Lorazepam 1 mg/mL in ORA-Plus®/ORA-Sweet® was prepared from lorazepam tablets, stored in amber glass bottles and both refrigerated at room temperatures and sampled at 2, 3, 7, 14, 21, 28, 42, 63 and 91 days. Results showed the suspensions were stable for 63 days at room temperature when prepared from the Watson Labs tablets and for 91 days for both the Watson Labs and Mylan brands when stored at refrigerated temperature and the Mylan tablet at room temperature. Results are shown in Table 7. Note that for the Watson Labs Brand at 22° C, at 63 days the mean was 90.9 and the standard deviation was 1.1; this makes the range from 89.8 to 92.0, outside the acceptable range of 90.0 to 100.0%. Therefore, the BUD for the Watson Labs brand at 22° C would only be 28 days according to the data (means +/- standard deviations).

Table 7: Stability of lorazepam 1mg/mL in ORA-Plus® and ORA-Sweet® prepared from two different brands of lorazepam tablets and stored at 4° C and 22° C.

Storage Temperature (° C)	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining 14 days	28 days	63 days	91 days
Mylan Brand					
4	0.98 (0.01)	100.1 (0.8)	101.3 (2.3)	97.0 (3.4)	96.8 (1.6)
22	0.98 (0.02)	101.0 (5.0)	99.3 (3.0)	94.0 (2.7)	94.2 (2.2)
Watson Labs Brand					
4	1.04 (0.01)	102.6 (2.8)	102.3 (1.5)	102.1 (2.1)	99.4 (2.7)
22	1.03 (0.01)	99.6 (1.2)	98.3 (1.7)	90.9 (1.1)	88.9 (1.4)

Methotrexate (C20H22N8O5, MW 454.44) occurs as an orange-brown or yellow crystalline powder that is practically insoluble in water. It is most stable at pH values of 6 to 8; extremes of pH should be avoided; it is not stable at a pH value less than 6.6. Methotrexate 2 mg/mL was prepared using methotrexate injection, sodium bicarbonate, ORA-Sweet® and sterile water for injection. The solutions were packaged in amber type I glass bottles for 120 days and stored at 4° C or 25°C . The preparations were stable throughout the duration of the study of 120 days. The pH remained stable at about 8 in all the formulations.

Metronidazole Benzoate (C13H13N3O4, MW 275.26) occurs as a white to slightly yellow, crystalline powder that is practically insoluble in water. Metronidazole benzoate 16 mg/mL in ORA-Plus® and a mixture of ORA-Plus®/ORA-Sweet® was prepared and stored at room temperature for up to 90 days. Metronidazole benzoate 16 mg/mL is approximately equivalent to metronidazole (MW 171.15) 10 mg/mL. The pH of the preparations was 4.3 (0.1). Table 8 presents the data showing that the preparations are stable for 90 days.

Table 8: Stability of metronidazole benzoate 16 mg/mL in ORA-Plus® or ORA-Plus®/ORA-Sweet® and stored at 25° C.

Formula	% Initial Concentration Remaining		
	33 days	60 days	90 days
ORA-Plus®	99.9	101.0	100.7
ORA-Plus®/ORA-Sweet®	100.8	100.1	99.7

Perphenazine (C21H26ClN3OS, MW 403.97) occurs as a white to creamy white, odorless powder that is practically insoluble in water. Perphenazine 0.5 mg/mL in ORA-Sweet® was prepared in two groups: Group 1 had an antioxidant (0.1% sodium metabisulfite) and Group 2 did not contain the antioxidant. The preparations were stored in amber colored glass bottles, stored at room temperature and sampled at 30, 62 and 90 days. The pH of the preparations was 3.7; citric acid (0.05%) was added to the formulation to assist in dissolving the perphenazine. Table 9 shows the results of the study indicating that perphenazine is stable for only 30 days in both of the preparations (with and without the antioxidant) when stored in amber glass containers at room temperature.

Table 9: Stability of perphenazine 0.5 mg/mL in ORA-Sweet® with and without added antioxidant and stored at 25° C.

Formula	% Initial Concentration Remaining		
	30 days	62 days	90 days
Without Antioxidant	91.5 (0.6)	83.3 (0.7)	75.2 (0.7)
With Antioxidant	94.4 (0.6)	87.8 (0.7)	80.1 (0.6)

REFERENCES

1. USP Pharmacopeia/National Formulary. U.S. Pharmacopeial Convention, Inc., Rockville MD, Current Edition

2. Prohotsky DL, Juba KM, Zhao F. Formulation and Stability of an Extemporaneously Compounded Oral Solution of Chlorpromazine HCl. J Pain & Palliative Care Pharmacotherapy. 2014;28:367-370.

3. Nahata MC. Development of Two Stable Oral Suspensions for Gabapentin. Pediatr Neurol 1999;20:195-197.

4. Gupta VD. Chemical Stability of Hydrocortisone in Humco Simple Syrup and Ora-Sweet Vehicle. IJPC 14(1) Jan/Feb 2010; 76-77.

5. Nahata MC, Morosco RS, Hipple TF. Stability of Lamotrigine in Two Extemporaneously Prepared Oral Suspensions at 4 and 25° C. Am J Health-Syst Pharm. 1999;56:240-2.

6. Ensom MHH, Decarie D, Rudolph S. Stability of Levetiracetam in Extemporaneously Compounded Suspensions. Can J Hosp Pharm. 2011 May-Jun;64(3): 207-211.

7. VandenBussche HL, Johnson CE, Fontana EM, Meram JM. Stability of Levofloxacin in an Extemporaneously Compounded Oral Liquid. Am J Health-Syst Pharm. 1999;56:2316-8.

8. Lee Wan-Man E. et al. Chemical Stability of Extemporaneously Prepared Lorazepam Suspension at Two Temperatures. J Pediatr Pharmacol Ther 2004;9:254-258.

9. Vrignaud S. et al. Design and Stability Study of a Paediatric Oral Solution of Methotrexate 2 mg/mL. Int'l J of Pharmaceutics 487(2015)270-273.

10. Mathew M, Das Gupta V, Bethea C. Stability of Metronidazole Benzoate in Suspensions. Journal of Clinical Pharmacy and Therapeutics (1994)19, 31-34.

11. Gupta VD. Chemical Stability of Perphenazine in Oral Liquid Dosage Forms. IJPC 9(6) Nov/Dec 2005, 484-486.