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Stability of Extemporaneously Prepared Oral Liquid Formulations - Part VII

GOALS AND OBJECTIVES

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. List specific issues to be addressed in reviewing stability studies,
2. Describe the aspects of a stability-indicating assay that should be present in a stability study,
3. Analyze the tabulated results and assign an appropriate beyond-use date, and
4. Discuss the conditions commonly used in stability studies for extemporaneously compounded preparations.

INTRODUCTION

In evaluating stability studies for appropriateness, it is important to check for specific topics to be addressed in the studies. A cardinal rule is that one of similar education and ability should be able to reproduce the results from the information provided in the published study. Some specific issues to address in stability studies of extemporaneous compounded preparations are as follows.

The complete composition and method of preparation of the formula must be presented. It is interesting that many studies in the medical literature about new formulations or new drugs don't provide the complete formulation information. Fortunately, most stability studies in the pharmaceutical literature now provide this information. The shortfall would be if nondescript ingredients such as "cherry syrup" are used without any qualifying information. Commercial products, such as Ora-Sweet®, are defined compositions and make it much easier.

The study design should have an initial (time-zero), at least one intermediate, and a final time point to aid in evaluation; additional reasonable intervals are recommended. Samples should be prepared at least in triplicate. The storage conditions for the samples must be described. Most commonly, room and refrigerated temperatures are used. It is of value to provide the actual temperatures.

The analytical method must be stability-indicating and appropriate for the study. The stability-indicating nature of the assay is usually done by force-degrading samples to about 50-75% loss of drug using a combination of heat, light, oxidizing agent, acid and/or base methods. The degradants should be well-separated from the intact drug for the study to be valid. Chromatograms should be provided of both intact and degraded drug.

The manufacturer and lot number of all ingredients should be provided. The ingredients used must be at least of USP or NF quality, if applicable. The equipment manufacturer and model should be specified; supplies should be well-described. The data on the calibration curve linearity, limit of quantification of the analyte,

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method of repeatability, intraday and interday coefficients of variation should be provided. Analytical replicates should not exceed a variation of 2% and any unusual results should be adequately explained.

Physical observations for any change in clarity (if a solution), color, and for suspensions, any change in settling, caking, resuspending, and for emulsions, creaming, layering, etc. Generally, the proposed beyond-use-date (BUD) shows less than about a 7% loss. The appropriate BUD is no longer than the length of the study. Any conclusions do not over-extend the data and are reasonable. The source of the drug must be specified; is it the bulk drug substance, capsules, tablets, injections, etc. as different excipients may affect the BUD.

For this issue, the individual drugs and concentrations reported here are shown in Table 1.

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

Drug	Concentration (mg/mL)
Aprepitant	20
Celecoxib	10
Clozapine	20
Cyclophosphamide	10
Dolasetron	10
Granisetron	0.05
Lansoprazole	3
Moxifloxacin	20
Rifaximin	20
Sunitinib	10

STABILITY OF EXTEMPORANEOUS FORMULATIONS

Aprepitant ($C_{23}H_{21}F_7N_4O_3$, MW 435.43, Emend®) occurs as a white to off-white crystalline solid that is practically insoluble in water; it is sparingly soluble in ethanol. The capsule contents also contain sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. It is used in the treatment of nausea and vomiting associated with cancer chemotherapy.[1]

The aprepitant 20 mg/mL oral liquid was prepared using 125 mg capsules (Emend, Merck & Co., Inc.), as follows.[2] The contents of the aprepitant capsules were emptied into a mortar and ground to a fine powder. A small amount of Ora-Blend® was added to the fine powder and triturated to a smooth paste. More Ora-Blend was added and the mixture transferred to a graduate. The mortar was rinsed with Ora-Blend and the mixture added to the graduate. Finally, sufficient Ora-Blend was added to final volume and mixed well. The mixture was placed in glass and polyethylene terephthalate (PET) bottles and stored at both 4 and 23° C. The aprepitant content of three test solutions of each container type and storage temperature was determined using stability-indicating assay at 5, 9, 14, 29, 48, 62, 73 and 111 days after compounding.

The mean pH values for the samples stored at room temperature and refrigerator were pH 4.27 (0.043) and 4.27 (0.032), respectively. The oral suspension under conditions in this study are stable for at least 90 days when refrigerated.

Table 2: Stability of aprepitant 20 mg/mL in Ora-Blend in glass and PET bottles stored at 4° C and 23° C.

	% Initial Concentration Remaining			
Time (days)	4° C: Glass	4° C PET	23° C Glass	23° C PET
0	22.0 (0.4)[a]	21.5 (1.3)[a]	22.0 (1.1)[a]	21.1 (0.5)[a]
5	97.1 (3.3)	99.8 (3.7)	100.0 (5.1)	100.0 (7.9)
14	97.6 (3.6)	102.1 (3.6)	101.0 (5.7)	112.1 (1.7)
29	103.1 (0.6)	106.8 (1.9)	108.7 (2.6)	109.2 (5.6)
48	97.7 (0.9)	101.1 (1.7)	106.7 (9.3)	106.4 (3.6)
73	107.0 (2.6)	NA	115.6 (6.5)	102.9 (6.5)
111	94.0 (6.8)	109.6 (11.7)	95.2 (3.9)	98.1 (3.5)

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

Celecoxib ($C_{17}H_{14}F_3N_3O_2S$, MW 381.37 Celebrex®) occurs as a pale yellow solid. It is a nonsteroidal anti-inflammatory agent. The capsule contents also contain croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone and sodium lauryl sulfate.[1]

Commercially available celecoxib capsules (Celebrex, Pfizer Canada Inc.) were used for the suspension. The contents of the capsules were ground to a fine powder in a mortar with a pestle. The powder was then suspended in Ora-Blend to final volume and mixed well. The suspension was placed into amber polyvinyl chloride (PVC) bottles and stored at 5° and 23° C.[3] Samples were collected initially and on days 7, 14, 21, 27, 56 and 93.

The pH range was 4.36 to 4.39 for refrigerated samples and 4.39 to 4.45 for the room temperature samples. The celecoxib suspension in Ora-Blend under conditions in this study was stable for at least 93 days in either room or refrigerated temperatures.

Table 3: Stability of celecoxib suspension 10 mg/mL in Ora-Blend in amber PVC bottles stored at both room and refrigerated temperatures.

	% Initial Concentration Remaining	
Time (Days)	23° C	5° C
0	10.1 (0.55)[a]	10.2 (0.35)[a]
7	98.9 (2.5)	99.2 (1.2)
14	100.8 (2.0)	98.9 (1.5)
21	100.2 (1.8)	97.8 (2.1)
27	97.8 (1.1)	96.8 (0.8)
56	98.1 (2.3)	97.5 (0.9)
93	99.4 (1.0)	94.6 (1.2)

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

Clozapine ($C_{18}H_{19}ClN_4$, MW 326.82 Clozaril®) occurs as a yellow, crystalline powder that is soluble in alcohol and insoluble in water. It is an antipsychotic drug that is generically available.

Clozapine 20 mg/mL suspension was prepared by suspending clozapine in either Ora-Sweet, Ora-Plus® or a 1:1 mixture of Ora-Sweet and Ora-Plus and packaged in low-density polyethylene (LDPE) amber containers and stored at room temperature. Sampling was done initially and on days 3, 6, 14, 28 and 63. The stability of clozapine under conditions in this study was determined to be 63 days at room temperature.[4]

Table 4: Stability of clozapine 20 mg/mL in Ora-Sweet, Ora-Plus or a 1:1 mixture of Ora-Sweet and Ora-Plus stored in LDPE amber containers at room temperature.

	% Initial Concentration Remaining		
Drug	Ora-Sweet	Ora-Plus	Ora-Sweet: Ora-Plus 1:1
0	19.98 (0.17)[a]	19.86 (0.18)[a]	19.84 (0.30)[a]
3	100.21 (1.52)	100.09 (2.95)	102.38 (2.56)
6	99.09 (1.54)	97.44 (6.19)	99.98 (1.72)
14	96.16 (1.72)	99.22 (2.39)	100.65 (1.90)
28	97.89 (2.12)	100.65 (0.79)	101.30 (1.82)
63	96.97 (1.85)	96.01 (0.70)	100.78 (0.63)

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

Cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P.H_2O$, MW 279.10 Cytoxan®) occurs as a white, crystalline powder that liquifies upon loss of its water of crystallization. It is soluble in water and in alcohol. Cyclophosphamide is a widely used chemotherapeutic drug for treating a wide range of malignancies. It is available as a lyophilized product containing cyclophosphamide and mannitol. Cyclophosphamide oral liquid was prepared by reconstituting cyclophosphamide injection with 0.9% sodium chloride injection to a concentration of 20 mg/mL. The solution was then mixed in a 1:1 ratio with Ora-Plus for a final concentration of 10 mg/mL. The mixtures were placed in amber polypropylene (PP) oral dispensing syringes and stored at either refrigerated or room temperature. Samples were obtained initially and on days 3, 7, 14, 21, 28, 35, 42, 49 and 56.[5]

Cyclophosphamide in Ora-Plus and stored at refrigerated temperature retained 98% of its initial concentration after 56 days of storage. At room temperature, the mixture degraded by 10% after only 6 days of storage. Therefore, this mixture should be refrigerated.

Dolasetron mesylate ($C_{19}H_{20}N_2O_3.CH_4O_3S.H_2O$, MW 438.49, Anzemet®) is an antiemetic that occurs as a white to off-white powder that is freely soluble in water and in propylene glycol and slightly soluble in alcohol. The tablets also contain carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, synthetic red iron oxide, titanium dioxide and white wax. They are printed with black ink, which contains lecithin, pharmaceutical glaze, propylene glycol and synthetic black iron oxide.[1]

The suspension was prepared by thoroughly crushing the dolasetron mesyltate tablets in a glass mortar. Ora-Plus and strawberry syrup or Ora-Plus with Ora-Sweet SF (1:1) were used as vehicles. The mixture was packaged in amber plastic bottles and stored at refrigerated and room temperatures. Sampling was done initially and on days 7, 14, 30, 60 and 90.[6]

At least 98% of the initial concentration of dolasetron mesylate remained throughout the 90 day study in all suspensions. There was no detectable changes in color, odor, or taste and no visible microbial growth in any sample. There was no appreciable change from the initial pH which was 4.10 for the strawberry syrup: Ora-Plus and pH 4.03 (0.03) for the Ora-Plus:Ora-Sweet® SF.

Table 5: Stability of dolasetron mesylate 10 mg/mL in Ora-Plus/Strawberry syrup or Ora-Plus:Ora-Sweet SF and packaged in amber plastic bottles stored at both room and refrigerated temperatures.

	% Initial Concentration Remaining			
Time (Days)	Ora-Plus: Ora-Sweet SF		Ora-Plus: Strawberry Syrup	
	Ref Temp	Room Temp	Ref Temp	Room Temp
0	9.91 (0.05)[a]	9.91 (0.05)[a]	9.94 (0.08)[a]	9.94 (0.08)[a]
7	99.61 (1.19)	99.41 (1.05)	99.34 (1.34)	100.61 (1.23)
14	99.83 (1.40)	98.75 (1.40)	100.00 (1.51)	100.40 (1.64)
30	99.58 (1.40)	100.17 (1.15)	99.87 (1.68)	99.83 (0.40)
60	100.01 (1.11)	99.82 (1.39)	99.57 (1.28)	99.82 (0.84)
90	99.08 (1.39)	100.46 (1.18)	99.34 (1.31)	99.54 (0.89)

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

Granisetron hydrochloride ($C_{18}H_{24}N_4O.HCl$, MW 348.87, Kytril®) is an antiemetic/antivertigo agent (a 5-HT_3 receptor antagonist) that occurs as a white to off-white solid that is readily soluble in water. It is generically available.

Granisetron hydrochloride 0.05 mg/mL oral suspension was prepared by crushing the tablets to a powder in a mortar. A 1:1 mixture of Ora-Sweet:Ora-Plus was used as the vehicle. The suspension was packaged in amber plastic prescription bottles and stored at refrigerator and room temperatures. Sampling was done initially and on days 7, 14, 28, 42, 56, 70 and 91.[7]

There was no change in pH or physical appearance over the study period. The initial and final pH values respectively for the Ora-Sweet:Ora-Plus preparation was 4.40 (0.03) and 4.40 (0.02) at 25° C and 4.42 (0.05) and 4.42 (0.07) at 4° C. The granisetron hydrochloride was stable for at least three months under the conditions used in this reported study.

Lansoprazole ($C_{16}H_{14}F_3N_3O_2S$, MW 369.36, Prevacid®) is a proton pump inhibitor that occurs as a white to brownish-white powder that is practically insoluble in water. It is available as delayed-release capsules that also contain hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar spheres, sucrose, polyethylene glycol, polysorbate 80 and titanium dioxide.

Table 6: Stability granisetron hydrochloride 0.05 mg/mL in Ora-Sweet:Ora-Plus packaged in plastic prescription bottles and stored at refrigerator and room temperatures.

	% Initial Concentration Remaining	
Time (Days)	**Room Temp**	**Ref Temp**
0	0.050 (0.002)[a]	0.050 (0.002)[a]
7	100.5 (2.6)	100.0 (2.2)
14	99.8 (3.0)	99.5 (1.5)
28	98.6 (2.8)	99.2 (2.3)
56	97.8 (3.1)	98.0 (3.0)
70	97.1 (3.5)	97.4 (3.5)
91	95.9 (4.2)	96.2 (4.2)

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

Lansoprazole 3 mg/mL oral suspension was prepared by mixing the contents of lansoprazole capsules (Abbott Laboratories, Saint-Laurent, Quebec) with equal parts of 8.4% sodium bicarbonate solution and Ora-Plus:Ora-Sweet (1:1) after adjusting the pH of this mixture to approximately 8.4 with 1N sodium hydroxide solution. The suspension was placed in amber glass prescription bottles and stored under both refrigerated and room temperature conditions. Samples were obtained initially and then weekly for up to 91 days.[8]

The pH of the suspensions was 8.84 (0.16) and 8.82 (0.17) respectively for the suspensions stored at 4° and 25° C respectively. There were no noticeable changes in pH odor or color. The lansoprazole 3 mg/mL suspensions were stable for up to 91 days under the conditions reported in this study.

Table 7: Stability of lansoprazole 3 mg/mL in a mixture of 1:1 sodium bicarbonate 8.4% solution with Ora-Plus:Ora-Sweet (1:1) packaged in glass bottles and stored at room and refrigerated temperatures.

	% Initial Concentration Remaining	
Time (days)	**Ref Temp**	**Room Temp**
0	2.886 (0.109)[a]	2.999 (0.129)[a]
7	102.2	90.7
14	101.1	102.1
28	94.9	91.6
56	101.1	92.2
91	93.9	103.0

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

Moxifloxacin hydrochloride ($C_{21}H_{24}FN_3O_4$.HCl, MW 437.89 Avelox®) is a fluoroquinolone antibiotic that occurs as a slightly yellow to yellow crystalline substance. The tablets also contain microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and ferric oxide.[1]

The oral suspension of moxifloxacin 20 mg/mL was prepared from moxifloxacin tablets. The tablets were triturated in a glass mortar to achieve a fine powder. The powder is passed through a sieve to remove any remnants of the enteric coating. The vehicle, consisting of a 1:1 mixture of Ora-Plus and either Ora-Sweet or Ora-Sweet SF was added to the powder and mixed vigorously. The mixture was packaged in amber plastic prescription bottles and stored at room temperature. Samples were obtained initially and after 7, 14, 28, 60 and 90 days.[9]

Moxifloxacin 20 mg/mL prepared in either Ora-Plus and Ora-Sweet (1:1) or Ora-Plus and Ora-Sweet SF were stable for at least 90 days under the conditions studied. The pH of the mixture was unchanged and was pH 4.29 (0.02) for the Ora-Sweet preparation and pH 4.36 (0.03) for the Ora-Sweet SF preparation.

Table 8: Stability of moxifloxacin 20 mg/mL in mixtures of Ora-Plus with Ora Sweet (1:1) or Ora-Plus with Ora-Sweet SF (1:1) in amber plastic bottles and stored at room temperature.

	% Initial Concentration Remaining	
Time (days)	**Ora-Plus: Ora-Sweet**	**Ora-Plus: Ora-Sweet SF**
0	20.06 (0.29)[a]	19.96 (0.10)[a]
7	100.17 (0.59)	99.95 (1.90)
14	99.56 (0.12)	100.16 (0.25)
28	100.05 (1.22)	99.93 (0.85)
60	100.97 (2.10)	102.46 (2.10)
90	99.97 (1.16)	100.71 (1.12)

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

Rifaximin ($C_{43}H_{51}N_3O_{11}$, MW 785.88, Xifaxan®) is an anti-infective agent that occurs as a red-orange powder that is soluble in alcohol and insoluble in water. The antibacterial is available as film-coated tablets that also contain colloidal silicon dioxide, sodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc and titanium dioxide.[1]

Rifaximin 20 mg/mL suspension was prepared from rifaximin tablets. The tablets were triturated in a glass mortar to a fine powder. The vehicle was prepared by mixing Ora-Plus 1:1 with either Ora-Sweet or Ora-Sweet SF. A portion of the vehicle was added to the powder and a smooth suspension formed. The mixture was then transferred to an amber plastic prescription bottle. Another portion of the vehicle was used to rinse the mortar and added to the bottle. Additional vehicle was added to volume and the contents mixed well. The mixture was stored at room temperature for the study. Samples were obtained initially and after 7, 15, 30 and 60 days.[10]

At least 99% of the initial concentration of rifaximin remained throughout the 60-day time period and there were no detectable changes in color, odor or taste. There was no visible microbial growth in any sample. There was no appreciable change in pH; pH 4.20 (0.03) with those made with Ora-Sweet and pH 4.32 (0.02) with those made with Ora-Sweet SF.

Table 9: Stability of rifaximin 20 mg/mL prepared in 1:1 mixtures of Ora-Plus with Ora-Sweet or Ora-Plus with Ora-Sweet SF, packaged in amber plastic prescription bottles and stored at room temperature.

	% Initial Concentration Remaining	
Time (Days)	Ora-Plus: Ora-Sweet	Ora-Plus: Ora-Sweet SF
0	19.92 (0.28)[a]	20.11 (0.40)[a]
7	100.75 (1.16)	100.38 (1.43)
15	100.52 (0.92)	99.03 (1.24)
30	100.32 (1.19)	100.30 (0.69)
60	100.79 (0.91)	99.68 (0.76)

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

Sunitinib malate ($C_{22}H_{27}FN_4O_2.C_4H_6O_5$, MW 532.56 Sutent®) is an anti-neoplastic agent that is available as Sutent capsules that also contain mannitol, croscarmellose sodium, povidone, magnesium stearate.[1]

Sunitinib malate 10 mg/mL was prepared from the capsules by mixing the contents of the capsules with a 1:1 mixture of Ora-Plus and Ora-Sweet. The suspensions were packaged in PET prescription bottles and stored at either refrigerated or room temperature. Sampling was done initially and at 1, 2, 3, 5, 7, 14, 21, 30, and 60 days.[11] The results showed that at both temperatures, the sunitinib retained greater than 96% of its initial concentration for 60 days under these study conditions with no change in color, consistency or odor. Mold or bacterial growth was not evident by visual inspection.

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