When Stability Study Testing Goes Wrong

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Background

Alberta Health Services (AHS) Pharmacy Services completed stability study testing to evaluate the stability of ibuprofen 40 mg/mL oral suspension in Oral Suspend and Oral Syrup prepared with powder.

Samples were compounded at the Kaye Edmonton Clinic and sent for stability testing at Applied Pharmaceutical Innovation (API). The study protocol would evaluate the stability of the suspension stored in polyethylene terephthalate (PETE) plastic bottles over 45 days at room temperature and under refrigeration.

Results

The study days for this protocol were days 0, 2, 7, 15, and 45. On each of these days the actual assay, pH, and appearance would be tested. The assay acceptance criteria as per USP <71> is 90 % to 110 % of the actual assay. For the ibuprofen 40 mg/mL oral suspension the acceptable concentration range based on the assay acceptance criteria would have been 36 mg/mL to 44 mg/mL.

On days 0, 2, and 7 actual assay results ranged from 33.9% to 210.7% as indicated in Tables 1 and 2. These assay results indicated concentrations of 13.6 mg/mL to 84.3 mg/mL, which was well outside of the allowable concentration range.

Table 1. ibuprofen oral suspension 40 mg/mL stored at room temperature

Day	Date Analyzed	Sample	Actual assay (90 - 110%) (± RSD)	pH (3.6 – 4.6)	Appearance *	Microbiology (USP <61> & USP <62>)
0	5-Dec-22	1a-1	210.7 ± n.d.**	4.3	Solids floating	-
		1a-2	70.1 ± n.d.	4.2	Solids floating	-
		1a-3	-	-	-	Conforms
2	07-Dec-22	1a-4	129.9 ± 0.03	4.1	Solids floating	-
		1a-5	64.3 ± 0.06	4.1	Solids floating	-
7	12-Dec-22	1a-6	113.1 ± 0.2	4.2	Solids floating	-
		1a-7	124.3 ± 0.02	4.2	Solids floating	-
15	-	1a-8≠	-	-	-	-
		1a-9≠	-	-	-	-
45	-	1a-10≠	-	-	-	-
	-	1a-11≠	-	-	-	-
	19-Jan-23	1a-12	-	-	-	Conforms

* Expected appearance white colour, homogeneous suspension, and no visible clumps
≠ Samples not analyzed because the study was suspended due to the failures
** n.d.: Not determined

Table 2. ibuprofen oral suspension 40 mg/mL stored under refrigeration

Day	Date Analyzed	Sample	Actual assay (90 - 110%) (± RSD)	pH (3.6 – 4.6)	Appearance *	Microbiology (USP <61> & USP <62>)
0	5-Dec-22	1b-1	33.9 ± n.d.**	4.2	Solids floating	-
		1b-2	45.4 ± n.d.	4.2	Solids floating	-
		1b-3	-	-	-	Conforms
2	07-Dec-22	1b-4	61.9 ± 0.02	4.1	Solids floating	-
		1b-5	57.0 ± 0.03	4.1	Solids floating	-
7	12-Dec-22	1b-6	97.6 ± 0.1	4.2	Solids floating	-
		1b-7	113.7 ± 0.02	4.2	Solids floating	-
15	13-Dec-22	1b-8≠	116.0 ± 0.01	4.1	Solids floating	-
		1b-9≠	141.9 ± 0.04	4.1	Solids floating	-
45	13-Dec-22	1b-10≠	145.6 ± 0.2	4.1	Solids floating	-
	13-Dec-22	1b-11≠	147.4 ± 0.1	4.2	Solids floating	-
	19-Jan-23	1b-12	-	-	-	Conforms

* Expected appearance white colour, homogeneous suspension, and no visible clumps
≠ Samples analyzed on day 8 because the study was suspended due to the assay failures
** n.d.: Not Determined

AHS Pharmacy Services met with the Applied Pharmaceutical Innovation team to discuss the results. The physical appearance was noted to have solids floating, and the suspension did not appear to be uniform, which was supported by the varying assay results.

AHS Pharmacy Services made the decision to cancel the remainder of the stability study. The room temperature portion of the study was completely cancelled, with no additional tests being completed after day 7. The remaining refrigerated samples were tested for assay and pH on day 8 and then the remainder of the stability study was cancelled.

With this information, AHS Pharmacy Services was left wondering what to do next.

Root Cause Analysis

When there is a sample that does not pass the testing acceptance criteria, a root cause analysis needs to be completed. A root cause analysis is the process of discovering the cause of the problem to identify appropriate solutions.

The Pharmacy Services team started the root cause analysis by looking at the information they had. The testing results indicated that the appearance of the solution was not homogenous as anticipated and had solids floating in all samples that were analyzed. The appearance, along with the assay, indicated unequal distribution of the active pharmaceutical ingredient within the suspension. The Pharmacy Services team looked to the compounding process and ingredients for answers.

The compounding process was reviewed, and inconsistencies were identified and investigated.

Issue: A glass mortar and pestle were used for trituration of the ibuprofen powder during stability testing. Glass mortar and pestles do not grind the powder as finely as ceramic types. Glass mortar and pestles are more suitable for mixing of liquids or creams. This may have led to the powder not being micronized as effectively.

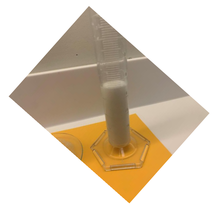
Investigation: A ceramic mortar and pestle were used for trituration of a sample ibuprofen batch.

Outcome: As you can see from the pictures below, the compounder was still unable to produce a uniform paste. The incorrect mortar and pestle did not appear to be the root cause.

Issue: The AHS compounding record that was used to complete the stability study testing did not include the same steps included in the referenced formulation. This may have led to inconsistent or inadequate mixing techniques which may have contributed to the non-homogenous suspension.

The AHS compounding record is instructions are indicated below, along with compounding pictures from a sample batch..

Gradually levigate powder with glycerin until a paste is formed.
Gradually add Medisca Oral Suspend until a liquid is formed.
Transfer into a graduated cylinder.



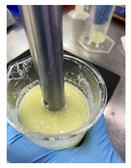
Investigation: A sample batch of ibuprofen was compounded following the reference formulation, which included high shearing mixing techniques.

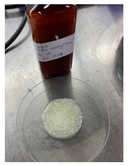
Outcome: The final product was still a non-homogenous suspension. The powder could still be seen floating in the suspension, and in the foam produced during compounding. The compounding process did not appear to be the root cause.

The reference formulation preparation instructions are indicated below, along with compounding pictures from a sample batch.

Preparatory Instruction

1. **Powder-liquid preparation:**
   A. Triturate the Ibuprofen to form a fine, homogeneous powder.
   B. Levigate the fine, homogeneous powder (Step 1A) with the Glycerin.
   End result: Homogeneous liquid-like dispersion.
2. **Medium integration:**
   A. In the given order, sequentially add the following ingredients to the Oral Mix (Flavored Suspending Vehicle) (45.0 mL *plus* processing error adjustments):
   -Tutti Frutti Flavor
   -Homogeneous liquid-like dispersion (Step 1B)
   Specifications: Continuously mix, using high-shear mixing techniques.
   End result: Homogeneous liquid-like dispersion.
   Note: Add the next ingredient, once the previous one has been completely added and dispersed.





Regardless of our compounding processes we were unable to produce a homogenous suspension, which led us to look at the active pharmaceutical ingredients and suspending agents.

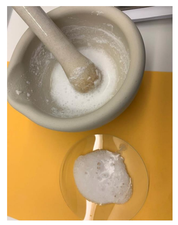
Issue: The certificate of analysis was not included within the stability study testing documentation. If the powder was not within appropriate specifications, it may have led to incorrect concentration of the suspension.

Investigation: A certificate of analysis was obtained for the ibuprofen powder used to compound, and it indicated that the powder was within specification limits. However, it also alerted us to the fact that the powder was hygroscopic. Since the bottle of ibuprofen powder, we were using to compound was previously opened, we procured a new bottles of powder and compared the two.

Outcome: The opened bottle of powder did appear to be clumpier than that new bottle, however still produced a non-homogenous suspension.

The brand of powder on hand did not seem to be the issue, but we started to wonder how other brands of powder, or other suspending agents would react.

Numerous samples were compounded with varying ingredients, and unfortunately, we were still unable to compound a homogenous suspension.


Ibuprofen powder in sterile water


Ibuprofen powder in Ora Blend


Ibuprofen powder in Oral Mix

Conclusion

The root cause analysis led us to the conclusion that the reference formulation was not an acceptable reference for our use. The ibuprofen powder did not seem to be able to be suspended in any solution. Alberta Health Services made the decision to no longer compound this medication due to the inability to produce a homogenous suspension.