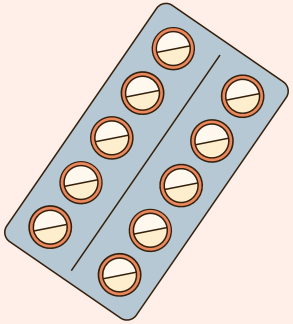
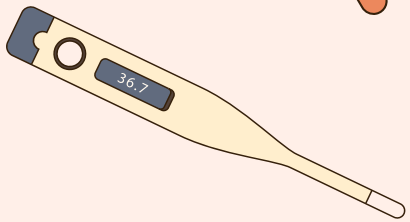




A Tale of Two Thieves

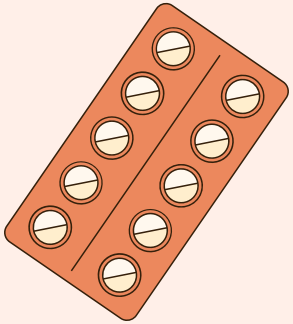
Mixed-Effects Model Analysis

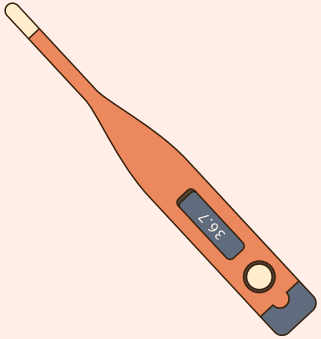
R14H41002 王敏行 統計學程

Executive Summary

This report analyzes two pharmaceutical sampling instruments, the Intermediate Dose (INTM) and Unit Dose (UNIT) thieves, to identify critical sources of product variability. While both methods produce statistically equivalent average results ($p = 0.307$), the INTM thief demonstrates far superior precision with a residual variance 4.81 times lower, making it the recommended tool for reliable quality control. More critically, the analysis reveals that the choice of instrument is secondary to fundamental manufacturing process flaws. The dominant source of product variability is a severe lack of mixture uniformity within the V-Blender, which accounts for 31.05\% of total variance. Furthermore, a systematic loss of approximately 3\% of the active ingredient occurs during the powder-to-tablet compression stage. Therefore, while adopting the INTM thief is advised, it is imperative that future process improvement efforts be prioritized on correcting these two core issues—blending uniformity and compression loss—to ensure final product quality.

TABLE OF CONTENTS





01 Introduction

Study Design

Manufacturing Process

The tablets are manufactured by

1. mixing **active** and **inactive** ingredients in a ``V-Blender."
2. After blending, the powder is **discharged** and **compressed** into tablets.

Requirement of this process is that the final tablets have **uniform content** →

correct amount of active ingredient is present in each tablet.

https://www.saintyco.com/pharma-equipment/solids-production-2/mixers/v-blender/

Sampling Instruments: Thieves

To assess the uniformity of the mixture ***before*** it is compressed, a ``thief'' instrument is used to obtain samples from different locations within the V-blender.

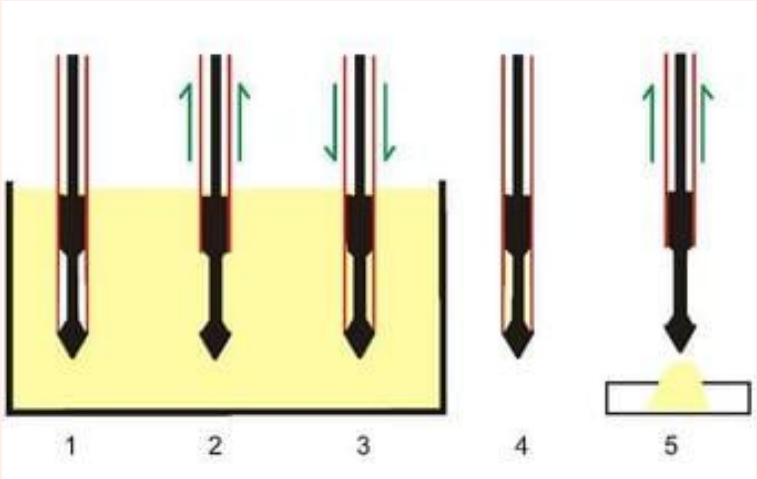
This study compares two types of thieves:

1. Unit Dose Thief
2. Intermediate Dose Thief

https://www.saintyco.com/pharma-equipment/solids-production-2/mixers/v-blender/

Method 1: Unit Dose Thief

This instrument collects **three individual unit** dose samples at each sampling location. This involves three separate sampling actions at the same spot.

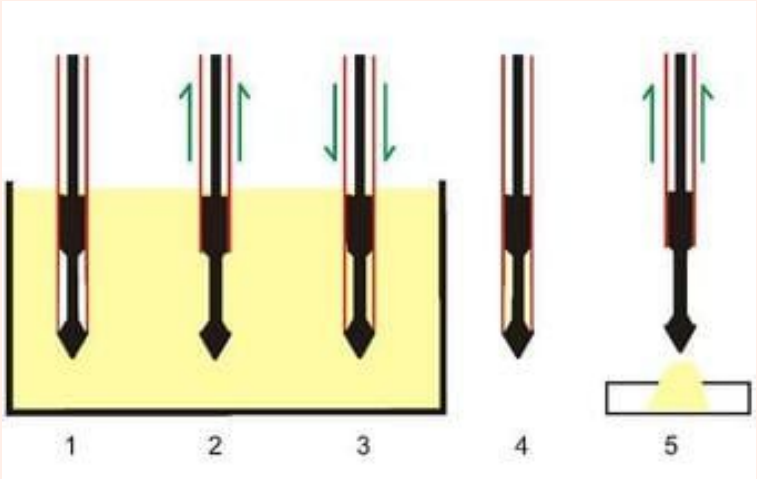


https://www.qclabequipment.com/publishImages/SAMPLERPOWDERTHIEF~~element783.jpg

Method 1: Unit Dose Thief

This instrument collects **one large sample at each location**.

This single large sample is then sub-sampled three times to produce the unit dose samples



https://www.qclabequipment.com/publishImages/SAMPLERPOWDERTHIEF~~element783.jpg

Method 1: Unit Dose Thief

Process (take Location 1 for example):

1. Arrive at Loc 1

Insert the sampler into the powder.

2. Sample A

Collect sample A, and then remove the sampler.

3. Sample B

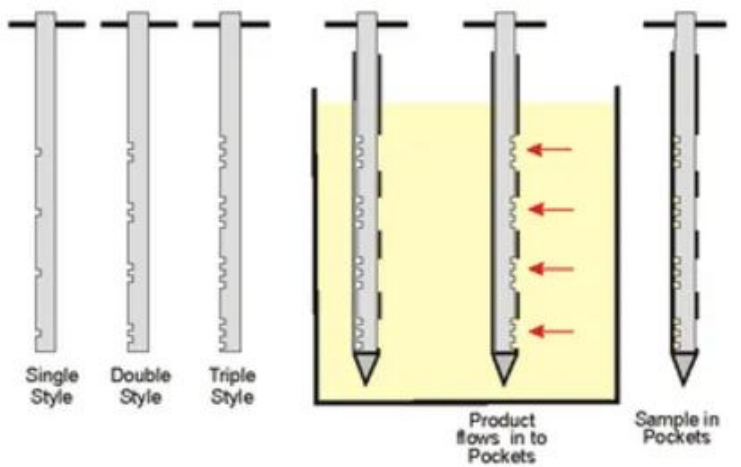
Re-insert the sampler, collect sample B, and then remove it.

4. Sample C

Re-insert again, collect sample C, and then remove it.

Method 2: Intermediate Dose Thief

This instrument collects **three individual unit** dose samples at each sampling location. This involves three separate sampling actions at the same spot.



https://www.qclabequipment.com/unitdosesamplethief.html?no_redirect=true

Method 1: Intermediate Dose Thief

Process (take Location 1 for example):

1. Arrive at Loc 1

Insert the sampler into the powder.

2. Sample a Large one

Collect one large sample, then remove the sampler.

3. Sub-sampling (External)

Dispense sample A, B, and C from this large sample.

Experimental Procedure

Step 1: Blend

- Put the powder of active and inactive ingredients into a large "V-Blender"
- Start the mixing tank and **rotate for 20 minutes** to ensure the powder is fully and uniformly mixed

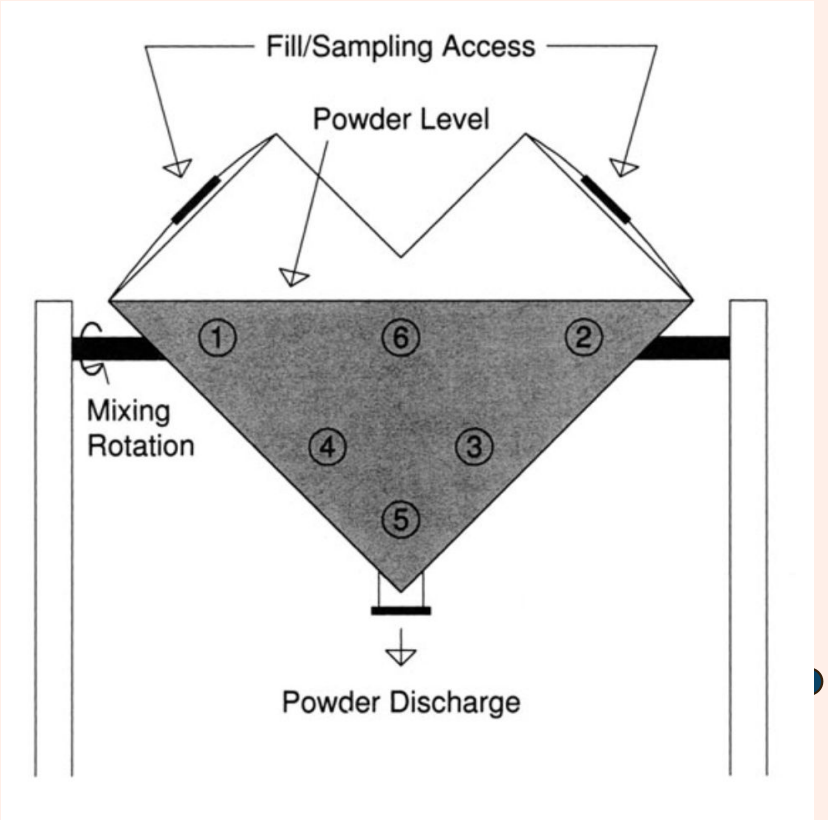
https://www.saintyco.com/pharma-equipment/solids-production-2/mixers/v-blender/

Step 2 Thief Sampling

The "Unit Dose Thief" and "Intermediate Dose Thief" are **tied together**.

- This "pair" of samplers is then sequentially inserted into **6** different locations within the mixing tank to collect samples.

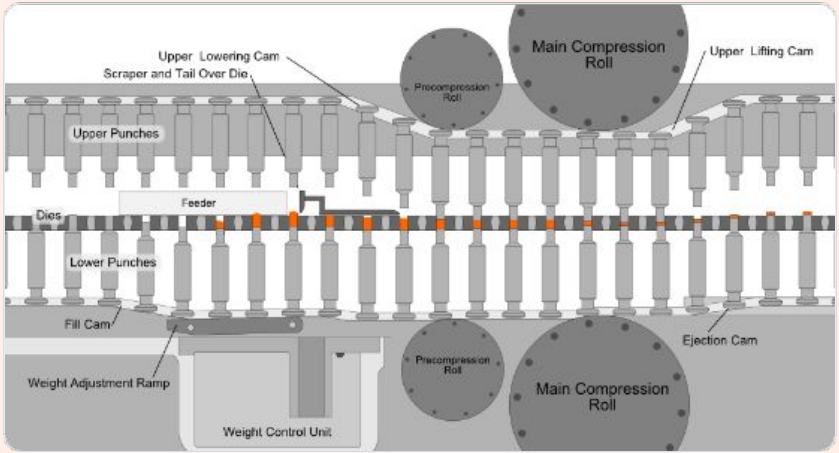
→ Tying them together ensures a **fair comparison under completely identical conditions**.



Cabrera, J., and McDougall, A. (2002) Statistical Consulting. Springer-Verlag New York, Inc., ISBN 978-1-4757-3663-2 (eBook).

Step 3 & 4

Step 3: Compress Tablets



The powder is discharged from the mixing tank and sent to the tablet press, where it is compressed into tablets and dispensed into **30 drums**.

https://upload.wikimedia.org/wikipedia/commons/5/5a/Tablet_press_animation.gif

Step 4: Sample Tablets

For a baseline comparison, **10 drums are randomly selected** from the 30 drums, and **3 tablet samples** are randomly drawn from each of these 10 drums.

https://image.slidesharecdn.com/coatingtabletppt-241001121051-d1a15e18/75/Tablet-Coating-Types-Coating-Materials-Coating-Pans-Industrial-Pharmacy-Ist-Theory-1-2048.jpg

https://www.qima.com/assets/0c6y4qslwvqw/7ifsFfWZmy8crliPjMiVs6/c840dba26560df5aab2efb4ea8777579/12_OrganischesLabor_0120_Web.jpg?fm=jpg&q=80&w=1920&fp=16%3A9%2C0.2044%2C0.1733%2C0.7956%2Cl&sv=3

Step 5 Assay

All samples collected during the experiment are sent to the laboratory for "Assay" (chemical analysis).

This includes:

- Powder samples collected by the **Thief** (from *Step 2*)
- **Tablet** samples drawn from the drums (from *Step 4*)

→ The purpose is to accurately measure the "**active ingredient content**" in each sample.





Variables

Variables

For this analysis, we examined data from both

- the ``**Thief**'' experiment and
- the final ``**Tablet**'' products.

Quantitative Measures:

Assay (Y) The response variable. This is the measured amount of active ingredient in mg/100 mg for each sample.

Variables

Categorical Factors - For Thief Data:

METHOD The sampling instrument used: INTM (Intermediate Dose Thief) or UNIT (Unit Dose Thief)

LOC The sampling location within the V-Blender: 1, 2, 3, 4, 5, 6

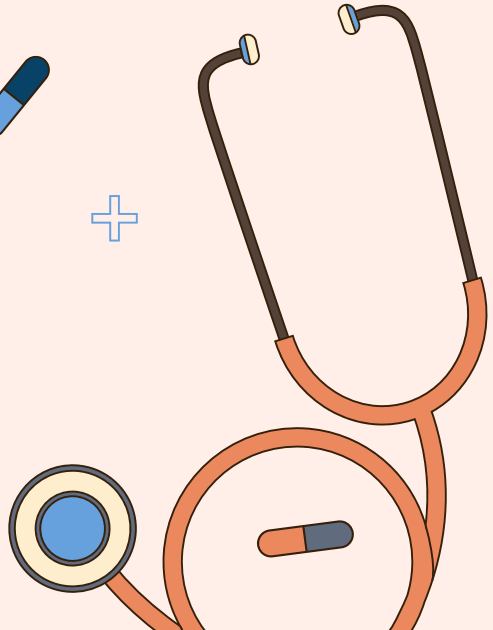
REP The replicate sample taken at each location: 1, 2, 3

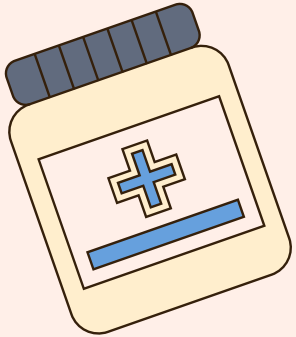
Categorical Factors - For Tablet Data:

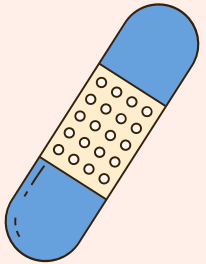
DRUM Randomly selected drums (10 out of 30 total drums)

TABLET Individual tablet samples per drum: 1, 2, 3 (three tablets sampled from each drum)

02 Methodology







Methodology

1 EDA

- Summary Statistics
- Plots: Parallel boxplots and location-specific comparisons

2 Mixed-Effect Model

- Fixed Effect
- Random Effect
- Precision Assessment (variance ratio: $\frac{\sigma^2_{\text{UNIT}}}{\sigma^2_{\text{INTM}}}$)

3 Regression Perspective

- Marginal R^2
- Conditional R^2

4 Interaction Analysis

- Random Slope Model

5 Model Assessment

- Diagnostic Check
- Effect Size Quantification
- Mean Comparison & Boostrapping

Review on ANOVA

METHOD Fixed, LOCATION Fixed

Model Specification:

$$\text{ASSAY}_{ijk} = \mu + \beta_i \cdot \text{METHOD}_i + \alpha_j + \gamma_{ij} + \varepsilon_{ijk}$$

Where:

- μ = Grand mean
- β_i = Fixed METHOD effect (INTM or UNIT)
- α_j = Fixed LOCATION effect ($j = 1, \ldots, 6$)
- γ_{ij} = Fixed METHOD $\times$ LOCATION interaction
- ε_{ijk} = Random error, $\varepsilon_{ijk} \sim N(0, \sigma^2)$

Mixed-Effect Model

METHOD Fixed, LOCATION Random

Model Specification:

$$\text{ASSAY}_{ijk} = \mu + \beta \cdot \text{METHOD} + b_i + \varepsilon_{ijk}$$

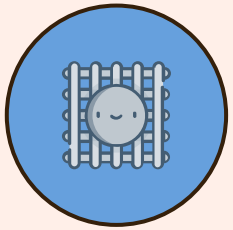
Where:

- μ = Grand mean
- β = Fixed METHOD effect (applies to any method)
- b_i = Random LOCATION intercept, $b_i \sim N(0, \sigma_b^2)$
- ε_{ijk} = Error term, $\varepsilon_{ijk} \sim N(0, \sigma_i^2)$

The difference

- Location is **RANDOM**
- Ignore the **Interaction** here

Mixed-Effect Model



Fixed Effect (METHOD)

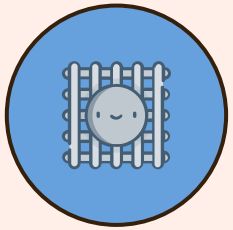
Research Question: Whether the Unit Dose (**UNIT**) and Intermediate Dose (**INTM**) thieves produce significantly different assay measurements (**hypothesis on mean**)→ **Typical ANOVA**

Random Effect (LOCATION)

Six sampling locations are a **random sample (Location random intercept)** from all possible locations within the blender.

Mixed-Effect Model

Regression Perspective



Marginal R^2 (METHOD)

Reflects the **variance explained by fixed effects (METHOD)** alone

$$R^2_{\text{Marginal}} = \frac{\text{Var}(\hat{\mu} + \beta \cdot \text{METHOD})}{\text{Var}(\text{ASSAY}_{ijk})}$$

Conditional R^2 (METHOD+LOCATION)

Reflects the variance explained by **both fixed effects (METHOD) and random effects (LOCATION)** combined

$$R^2_{\text{Conditional}} = \frac{\text{Var}(\hat{\mu} + \beta \cdot \text{METHOD} + b_i)}{\text{Var}(\text{ASSAY}_{ijk})}$$

Random Slope Model

Allowing METHOD Effects to Vary by Location

Model Specification:

$$\text{ASSAY}_{ijk} = \mu + (\beta + b_{i,\text{METHOD}}) \cdot \text{METHOD} + b_i + \varepsilon_{ijk}$$

Where:

- β = Global METHOD effect (fixed)
- b_i = Location-specific random intercept
- $b_{i,\text{METHOD}}$ = Location-specific METHOD effect (random slope)
- ε_{ijk} = Random error term

$$b_i \sim N(0, \sigma_b^2)$$
$$b_{i,\text{METHOD}} \sim N(0, \sigma_{b,\text{METHOD}}^2)$$
$$\varepsilon_{ijk} \sim N(0, \sigma_i^2)$$

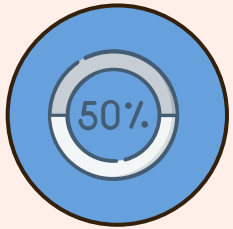
Does METHOD effect vary by location?

- If **No**: Basic Mixed Model
- If **Yes**: Random Slope Model

Model Assessment

Diagnostic Checks

- Q-Q plots / Shapiro test (normality check)
- Residuals vs. Fitted values (homoscedasticity)
- Cook's distance (influential outliers)

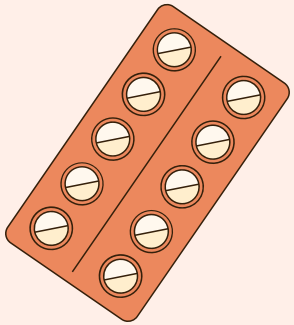


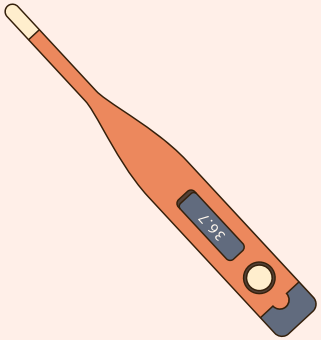
Effect Size Quantification

- Cohen's d
- Eta-squared η^2
- Omega-squared ω^2

Bootstrap Validation for Robustness

- 1000 resamples





03 Results

EDA

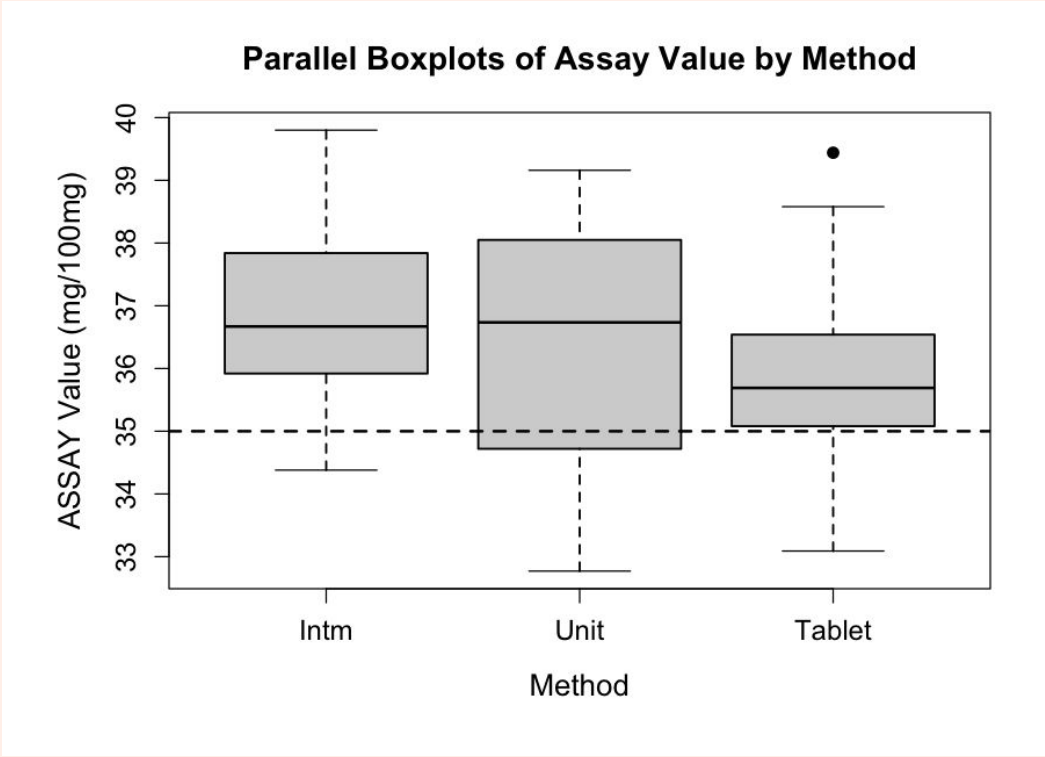
Summary Statistics

Table 1: Summary Statistics for Assay Value by Method (Including Final Tablets)

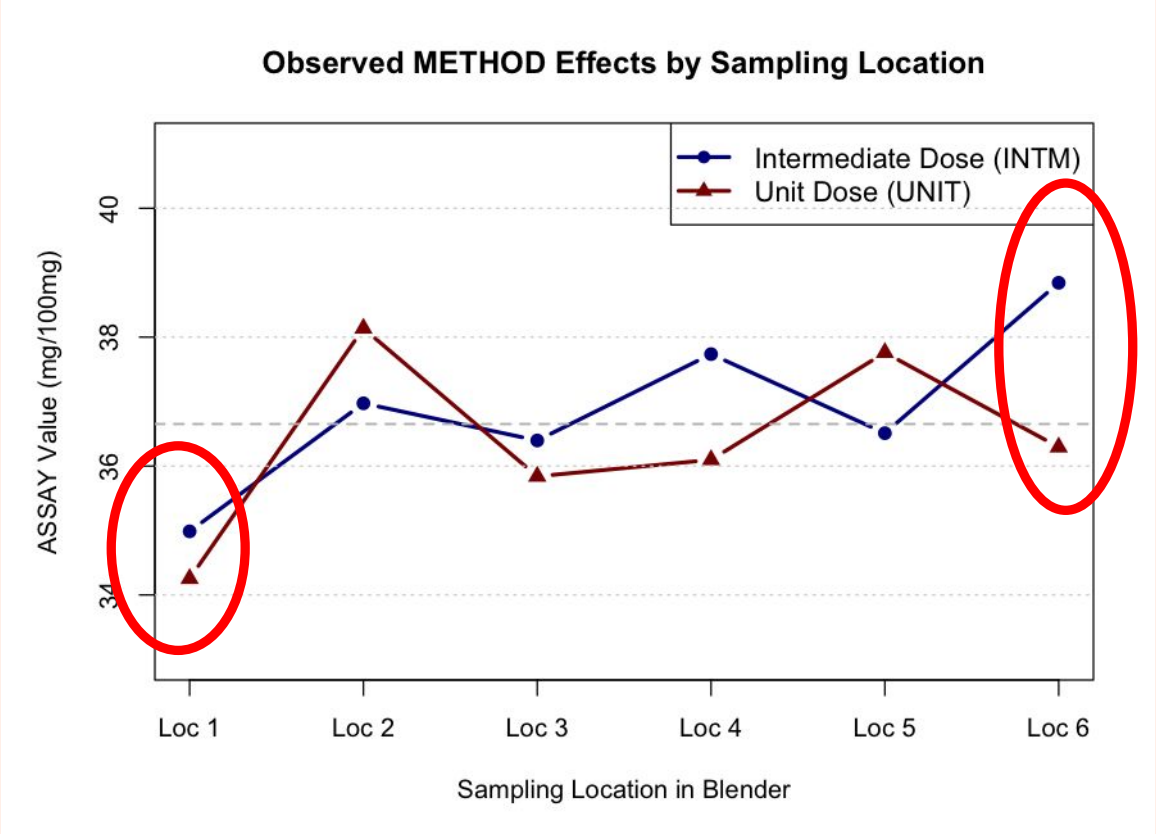
Method	N	Mean	SD	Min	Q1	Median	Q3	Max
Unit Dose (UNIT)	18	36.40	1.98	32.77	34.74	36.74	37.98	39.16
Intermediate Dose (INTM)	18	36.91	1.40	34.38	36.01	36.67	37.83	39.80
Tablet (Final Product)	30	35.82	1.33	33.09	35.10	35.69	36.52	39.44

Assay Distributions by Method

Parallel Boxplots



Assay Values Across Locations



Mixed-Effect Model

Mixed-Effects Model Summary

```
Linear mixed-effects model fit by maximum likelihood
  Data: thief_data
       AIC      BIC    logLik
  138.8111 146.7287 -64.40556

Random effects:
 Formula: ~1 | LOCATION
        (Intercept) Residual
StdDev:   0.9988227 0.840748

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | METHOD
 Parameter estimates:
  Intm   Unit
1.0000 2.1932
```

```
Fixed effects:  ASSAY ~ METHOD
                Value Std.Error DF  t-value p-value
(Intercept) 36.90778 0.4665138 29 79.11401   0.000
METHODUnit  -0.51111 0.4915120 29 -1.03988   0.307
 Correlation:
            (Intr)
METHODUnit -0.181

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.68564601 -0.46940828  0.04519855  0.62351689  1.86352013

Number of Observations: 36
Number of Groups: 6
```

The METHOD effect is NOT significant

Variance Components

Heterogeneous Variance Model

Table 4: Variance Components Decomposition

Variance Component	Estimate	Percentage	Interpretation
Between-Location [$\mathrm{Var}(b_i)$]	0.9976	31.0539%	Location-to-location variability
Within-Location, INTM [$\mathrm{Var}(\varepsilon_{ijk})$]	0.7069	–	Residual - Intermediate Dose
Within-Location, UNIT [$\mathrm{Var}(\varepsilon_{ijk})$]	3.4001	–	Residual - Unit Dose
Within-Location, Pooled [$\overline{\mathrm{Var}(\varepsilon_{ijk})}$]	2.0535	66.6436%	Weighted average residual
METHOD Effect [$\mathrm{Var}(\beta \cdot \mathrm{METHOD})$]	0.0672	2.3025%	Fixed effect variance
Total Variance	**2.9175**	**100.0%**	

The METHOD effect is NOT significant

Within-Location Variance

Precision Assessment

$$\text{Variance Ratio} = \frac{\sigma^2_{\text{UNIT}}}{\sigma^2_{\text{INTM}}}$$

Within-Location Variance of

- **Unit**: 3.4001
- **INTM**: 0.7069

Variance ratio = 3.4001 / 0.7069 = 4.81

→ Manufacturer's Perspective: **INTM is much more precise**

Between-Location Variance

Blending Uniformity

Between-Location Variance (Residual Variance) is

31%

of total variance

→ Mixture Uniformity is a concern

(Further Discussion in Question 2)

Regression Perspective

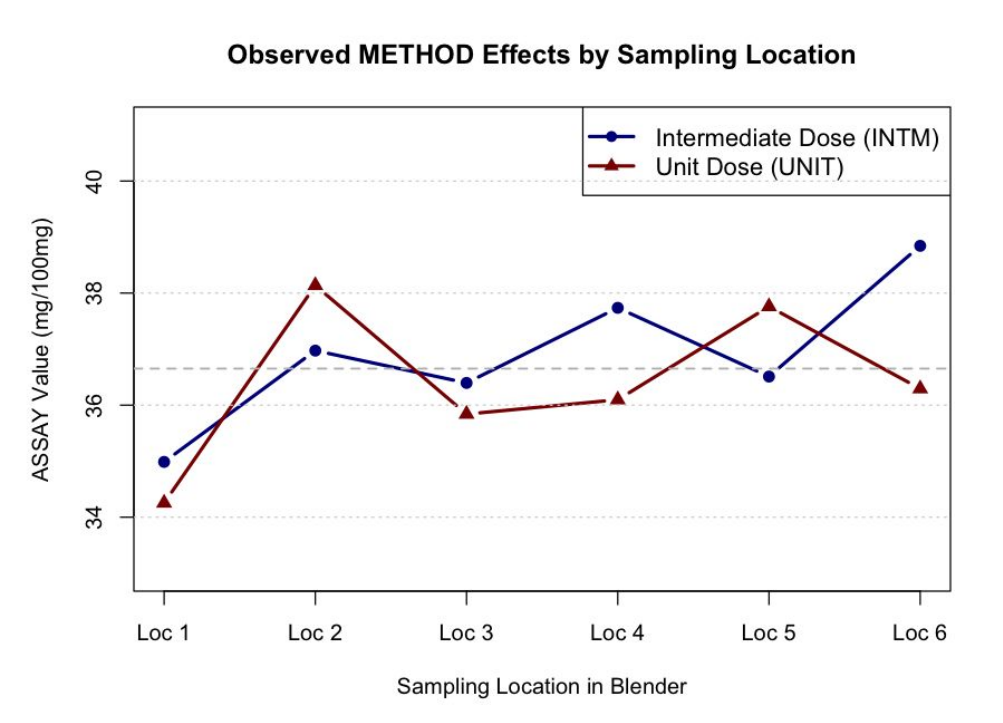
Heterogeneous Variance Model

Table 6: R^2 Decomposition and Variance Component Mapping

R^2 Measure	Value	Interpretation & Table A.3 Connection
Marginal R^2 (METHOD only)	2.3025%	Fixed METHOD effect (see Table A.3, row 5)
Conditional R^2 (METHOD + LOCATION)	33.3564%	Marginal + Random LOCATION effects
Variance Component Decomposition:		
METHOD Effect	2.3025%	Marginal R^2 (Table A.3)
LOCATION Effects	31.0539%	Conditional R^2 – Marginal R^2
Residual Error	66.6436%	1 – Conditional R^2

Interaction Analysis

Cross patterns → Interaction?



Interaction Analysis

Random Slope Model

Table 7: Likelihood Ratio Test: Random Slopes Model vs. Base Random Intercept Model

Model	df	AIC	BIC	Test	L.Ratio	p-value
mixed_model	5	138.8111	146.7287			
mixed_interaction	7	141.5994	152.6840	1 vs 2	1.211742	0.5456

The Interaction effect is NOT significant

Though the plot shows some crossing patterns:

- Limited sample size (n = 3 per location-method)
- Observed variability could be random fluctuation

→ Insufficient evidence to conclude location-dependent effects exist

Model Assessment

Diagnostic Checks

Data Quality

Normality test on data

Shapiro-Wilk Test

Both are normal:

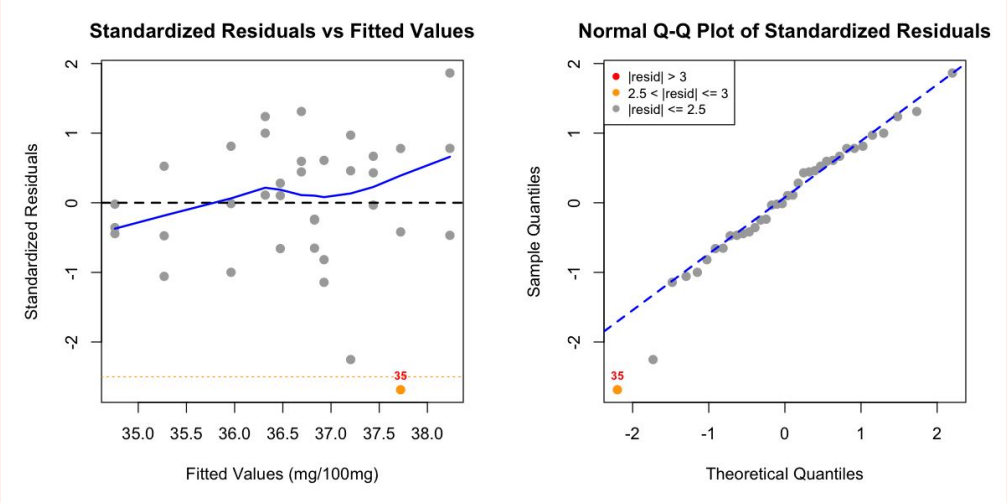
- INTM: p = 0.9794
- UNIT: p = 0.3190

Outliers

No outliers outside of Q3 + 2 x IQR

Cook's Distance: One identified

Model Assumption



Normality test on residuals

Shapiro-Wilk Test

- All residuals combined: p = 0.02337 → **Non-Normal**
- INTM method residuals: p = 0.7511 → **Normal**
- UNIT method residuals: p = 0.1842 → **Normal**

Effect Size

0.3	2.3%	0.28%
Cohen's d	Eta-squared	Omega-squared

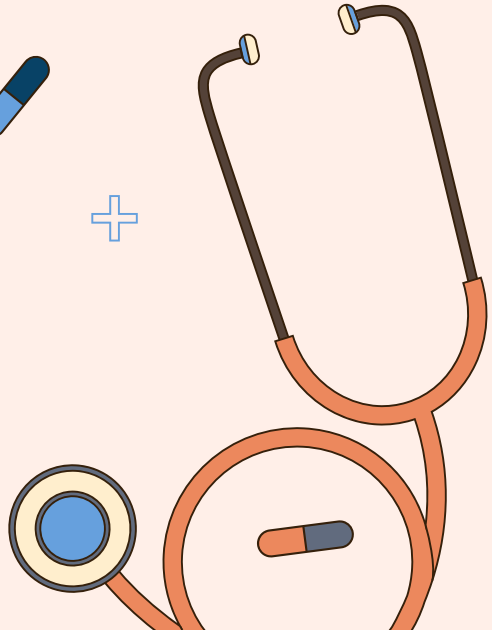
All these three measures show that the effect size is

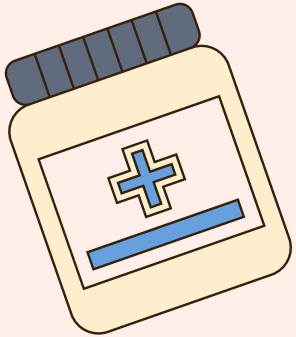
small

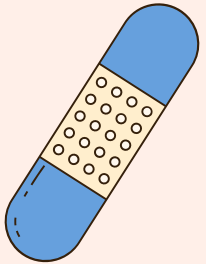
Negligible for manufacturing decision-making

04

Client Question Analysis







Q1 Are the assay values generally well behaved?

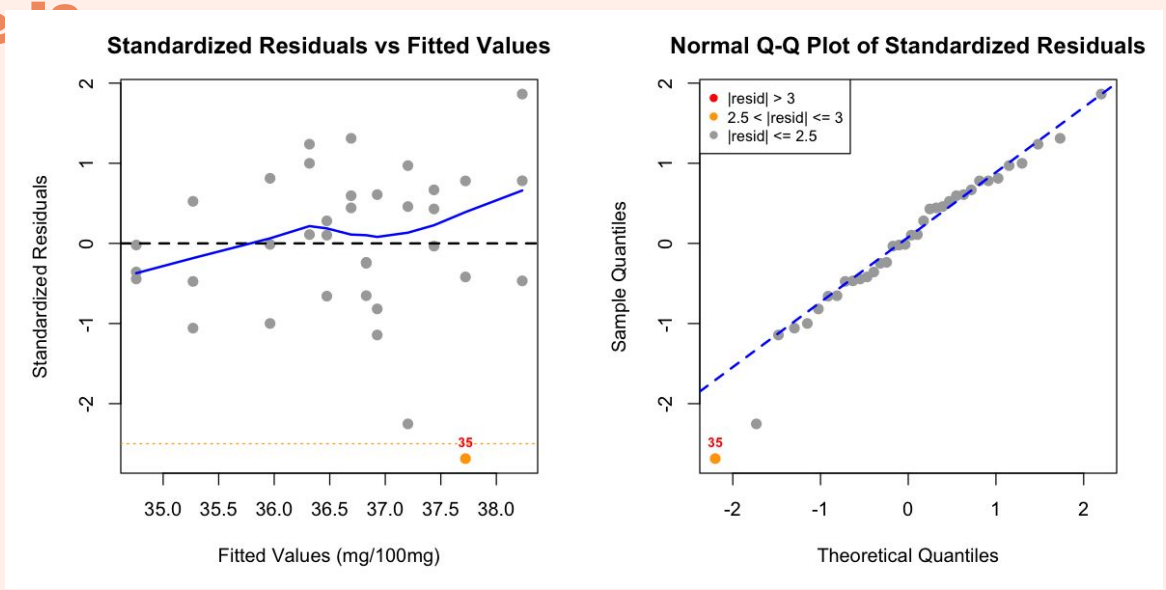
Client: Are the assay values generally well behaved? Note that when we treat the Thief samples as repeated measures, the issue of correlation needs to be incorporated in the criteria for determining outliers. Find out what procedures or tests are available and apply them to these data.

Traditional Methods: IQR (ignores the repeated measures)

Methods We Use:

- **Standardized Residuals** from Mixed Model
- **Cook's Distance**

Q1 Are the assay values generally well behave

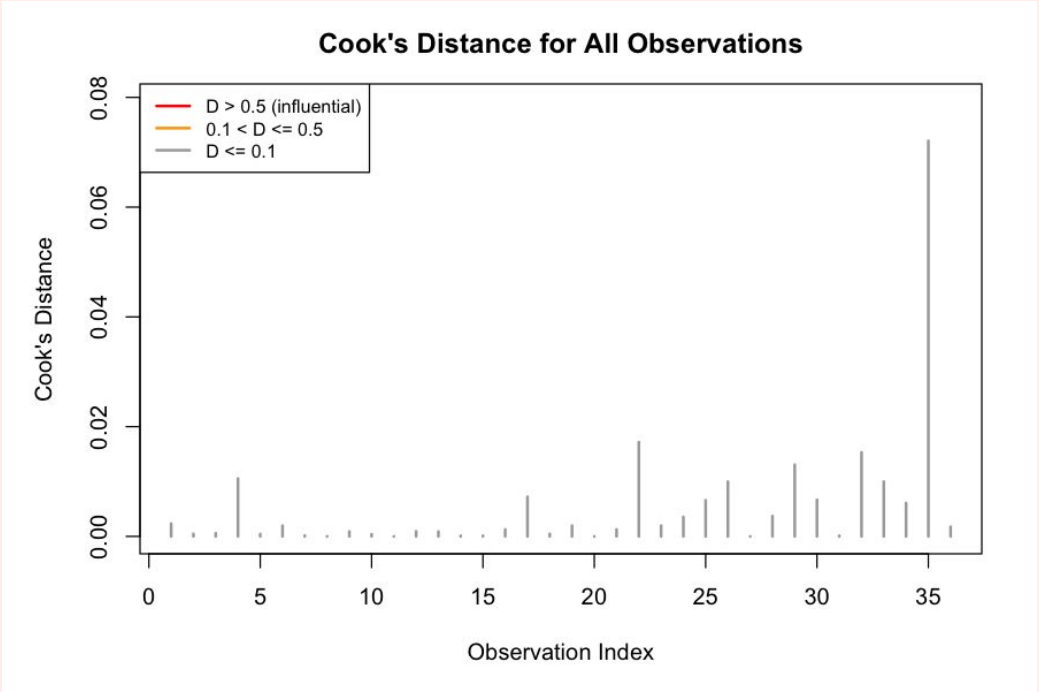


Standardized Residuals from Mixed Model: Extract residuals accounting for both fixed effects (METHOD) and random effects (LOCATION), then standardize. Observations with |residual| > 3 are flagged.

Q1 Are the assay values generally well behaved?

Cook's Distance: Identifies influential observations by measuring their impact on fitted values when deleted. Cook's distance combines two components:

- **Residual component:** How extreme is the observation's residual? (similar to standardized residual)
- **Leverage component:** How isolated is this observation in the predictor space? High leverage means the observation has disproportionate influence on parameter estimates.



Q2 Is there evidence of a location effect?

Client: Is there any evidence of a location effect? Our preliminary analysis suggests there is, which would be of concern to the production management. What recommendations should we make in our report to management regarding this issue?

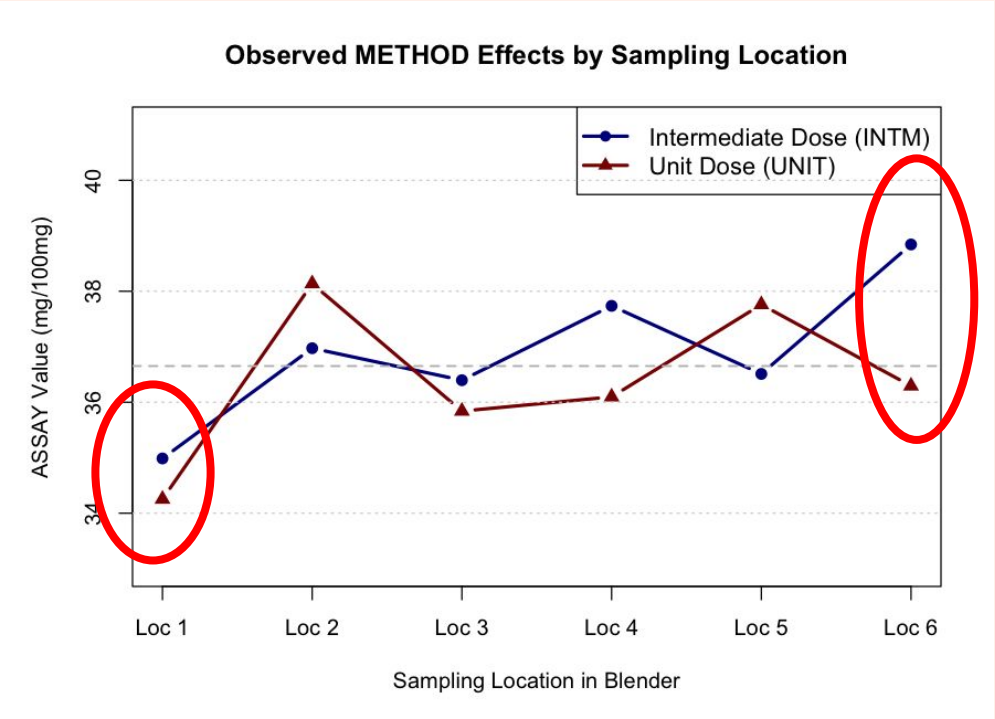
Evidence 1: Between-Location Variance (Residual Variance) is

31%

of total variance (from previous results)

Q2 Is there evidence of a location effect?

Evidence 2: Specific significant location differences



Q2 Is there evidence of a location effect?

Evidence 2: Specific significant location differences

Loc	Random Intercept	Loc	Relative Deviation (%)	z-score	p-value	Status
1	-1.64	35.01	-4.47	-2.801	0.0051	Significantly lower
2	+0.30	36.95	+0.81	+0.506	0.6130	Not significant
3	-0.43	36.22	-1.18	-0.742	0.4581	Not significant
4	+0.53	37.18	+1.45	+0.907	0.3642	Not significant
5	-0.08	36.57	-0.22	-0.135	0.8923	Not significant
6	+1.33	37.98	+3.62	+2.266	0.0235	Marginally higher

Q2 Suggestions

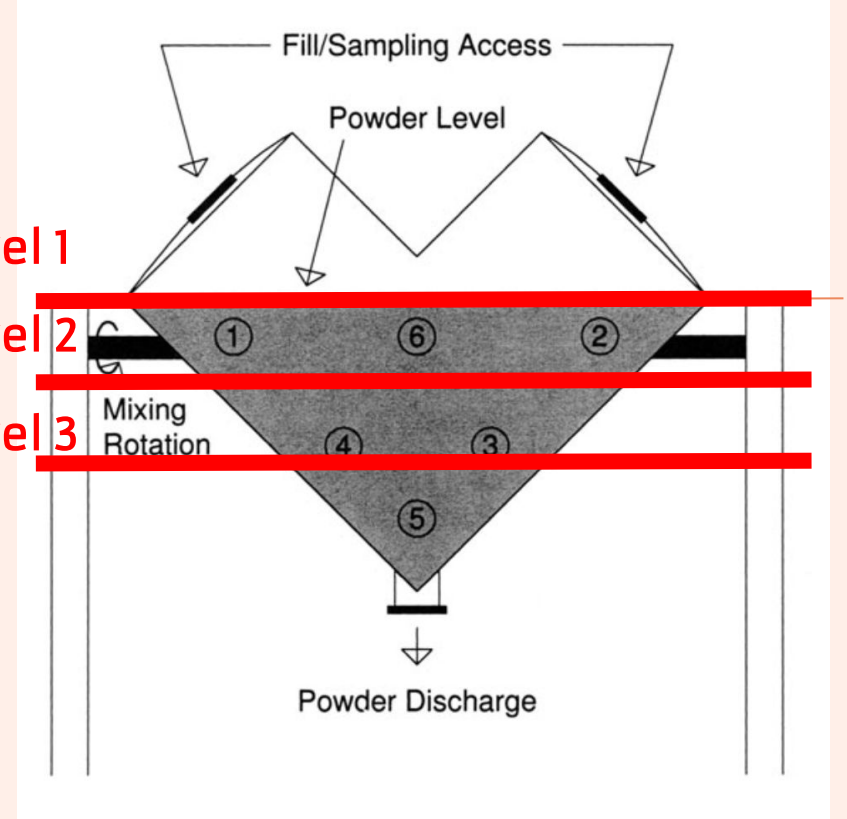
1. **Review mixing time adequacy**

Eg. Compare 20 / 40 / 60 minutes and sample on Loc1 and Loc6

2. **Conduct fill level experiment**

Eg. 40%, 60%, 80%

3. **Audit powder loading sequence**



Cabrera, J., and McDougall, A. (2002) Statistical Consulting. Springer-Verlag New York, Inc., ISBN 978-1-4757-3663-2 (eBook).

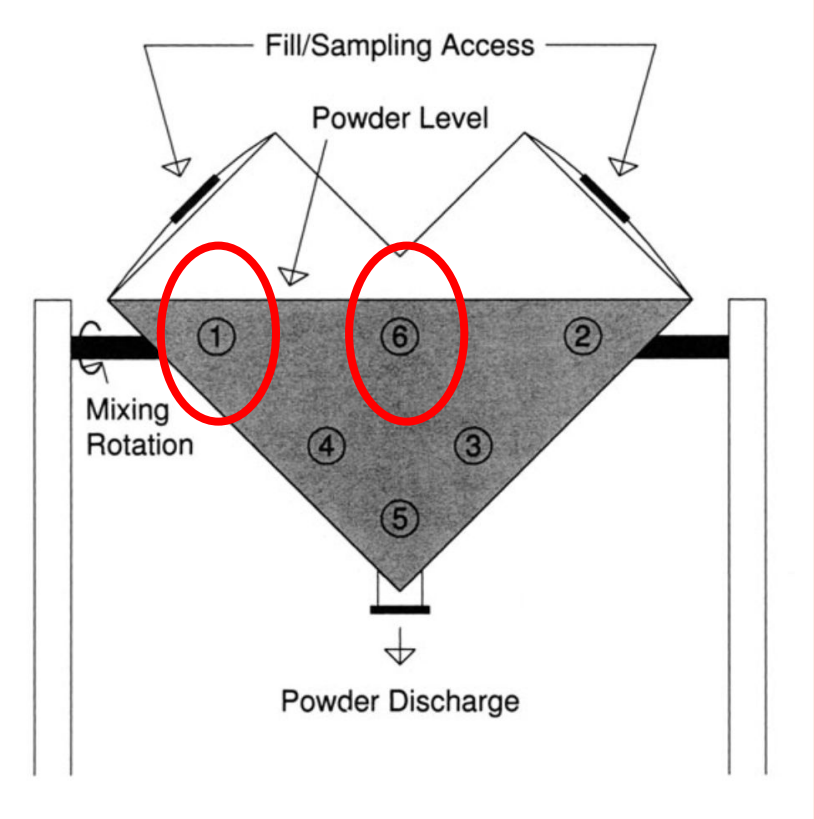
Q2 Suggestions

4. Assess blender geometry for dead spot

See the image: Why Loc 1 underestimates and Loc 6 overestimates?

5. Examine other factors

Eg. Mixer rotation speed, direction, or mechanical wear.



Cabrera, J., and McDougall, A. (2002) Statistical Consulting. Springer-Verlag New York, Inc., ISBN 978-1-4757-3663-2 (eBook).

Q3 Do the tablet data show any drum or time effect?

Client: Do the tablet data show any drum or time effect? We employed an autoregressive AR(1) covariance structure in the last proc mixed procedure for this purpose. Is this the same as using the Durbin-Watson test?

Drum effect? Relatively Small!

Evidence 1: Low Coefficient of Variance (0.6639/35.82=1.85%)

Mean ASSAY	35.82 mg/100mg	Overall tablet mean
Drum Standard Deviation	0.6629 mg/100mg	Between-drum SD
Coefficient of Variation (CV)	1.85%	Relative variability

Q3 Do the tablet data show any drum or time effect?

Evidence 2: Drum-to-Drum Variance Decomposition for Tablet Data

Variance components estimated using REML (Restricted Maximum Likelihood) method

with

Variance Component		Estimate	Interpretation
Between-Drum Variance	24.2%	0.4394	Drum-to-drum variability
Within-Drum (Residual) Variance	75.8%	1.3729	Tablet-to-tablet variability
Total Variance		1.8123	Sum of variance components

Tablet-to-Tablet Variation > Drum-to-Drum Variation

(Within-Drum Variance) > (Between-Drum Variance)

Q3 Do the tablet data show any drum or time effect?

Time effect? Not significant

Evidence 1: Independence vs. AR(1) Covariance Structure

Table 15: Model Comparison: Independence vs. AR(1) Covariance Structure

Model	df	AIC	BIC	Test	L.Ratio	p-value
Independence (GLS)	2	105.45	108.25	—	—	—
AR(1) (GLS+Correlation)	3	106.04	110.24	1 vs 2	1.412	0.235

Independent GLS is enough

→ Time correlation is not significant

Q3 Do the tablet data show any drum or time effect?

Evidence 2: Durbin-Watson Test

A post-hoc diagnostic for detecting first-order autocorrelation in model residuals.

The Durbin-Watson statistic ranges from 0 to 4

- **DW ≈ 2** indicating **no autocorrelation**
- DW < 2: positive autocorrelation
- **DW > 2**: negative autocorrelation

Table 16: Durbin-Watson Test for First-Order Autocorrelation

Statistic	Value
DW Statistic	1.565
p-value	0.077
Alternative Hypothesis	True autocorrelation > 0
Interpretation	No significant autocorrelation

Though 0.077 > 0.05 is NOT significant, still need to be cautious that Tablets might be **negatively autocorrelated**

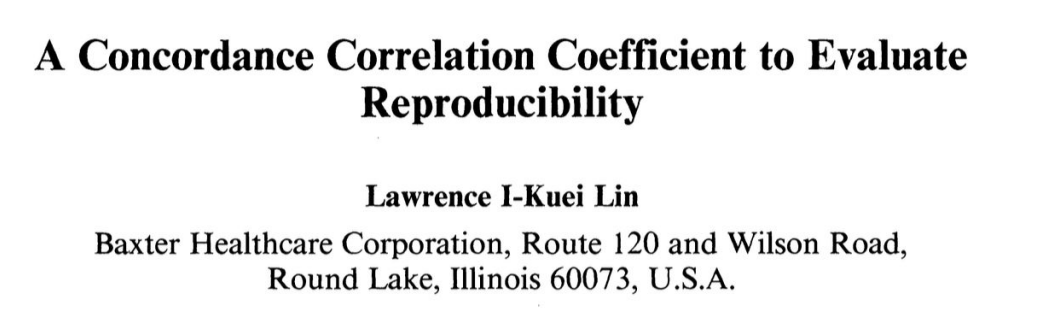
Q3 Comparison

Durbin-Watson Test vs AR(1)

	Durbin-Watson Test	AR(1) Model
Nature	Diagnostic Tool	Modeling Method
Timing	Post-estimation (Checks residuals *after* model is run)	Model Specification (Incorporated *during* modeling)
Function	**Detects** the *presence* of autocorrelation	**Models** and *accounts for* the autocorrelation
Result	DW Statistic + p-value (Tells you "if" you have a problem)	Estimates ρ + Adjusts standard errors (Actively "adapts" the problem)

Q4 Are the thief-sampled values comparable to the tablet values?

Client: One approach would be to consider the concordance correlation coefficient proposed by Lin (1989): quantify the agreement between two readings from the same sample by measuring the variation from the 45° line through the origin.



A Concordance Correlation Coefficient to Evaluate Reproducibility

Lawrence I-Kuei Lin

Baxter Healthcare Corporation, Route 120 and Wilson Road, Round Lake, Illinois 60073, U.S.A.

Lin suggests the **sample should be paired**

→ **Two** Thieves and Tablets are not in the same sampling process

→ We can only compare means by **Welch t-test** and **Bootstrapping**

Welch t-test

Table 10: Welch's t-Test Results for Pairwise Comparisons

Comparison	Mean Diff	t-statistic	df	p-value	95% CI Lower	95% CI Upper
UNIT vs. INTM	-0.51	-0.895	30.627	0.3777	-1.676	0.654
UNIT vs. Tablet	0.58	1.102	26.416	0.2802	-0.500	1.660
INTM vs. Tablet	1.09	2.659	34.572	0.0118	0.258	1.924

Note: Mean differences calculated as (Group 1 Mean) - (Group 2 Mean). Negative values indicate Group 1 mean is lower than Group 2.

Bootstrap Validation

Table 11: Bootstrap Assessment of P-Value Reliability (1000 resamples)

Comparison	Observed P	Bootstrap Mean	Bias	Std Error
UNIT vs. INTM	0.3777	0.3744	-0.0033	0.2942
UNIT vs. Tablet	0.2802	0.3413	0.0610	0.2986
INTM vs. Tablet	0.0118	0.0556	0.0438	0.1253

The conclusion that **the means have no significant differences** for bootstrapping is stronger than t-test because it is robust non-parametric comparison of means

Implication

Comparison	Mean difference	Observed P	Bootstrap Mean
INTM vs. Tablet	1.09	0.0118	0.0556

The INTM vs Tablet bootstrap mean (p = 0.0556) remains close to the conventional 0.05 threshold →
Observed mean difference of **1.09 mg/100mg:**

Potential **active ingredient loss** during the powder-to-tablet compression process of approximately **3%**
(INTM: 36.91 mg/100mg vs Tablet: 35.82 mg/100mg)

Three Key Findings

1. Methods equivalent for mean estimation

Both sampling methods produce **statistically equivalent mean assay results**

→ either method is acceptable for average batch-level assessment.

2. Higher Precision for INTM

The Intermediate Dose method (INTM) exhibits **4.81 times lower residual variance**

→ INTM provides superior consistency critical for process monitoring

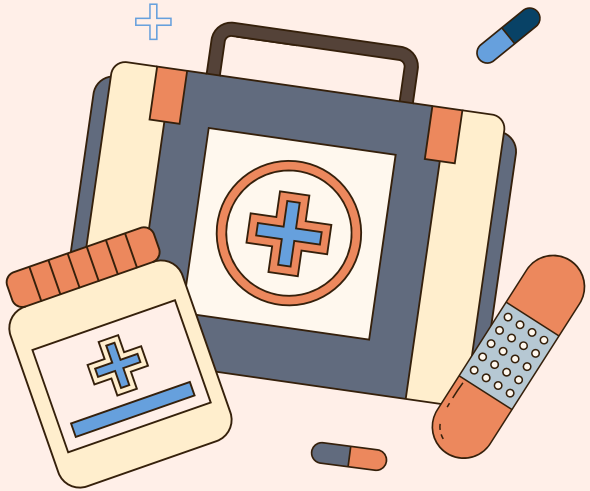
3. Location Effect > Method effect

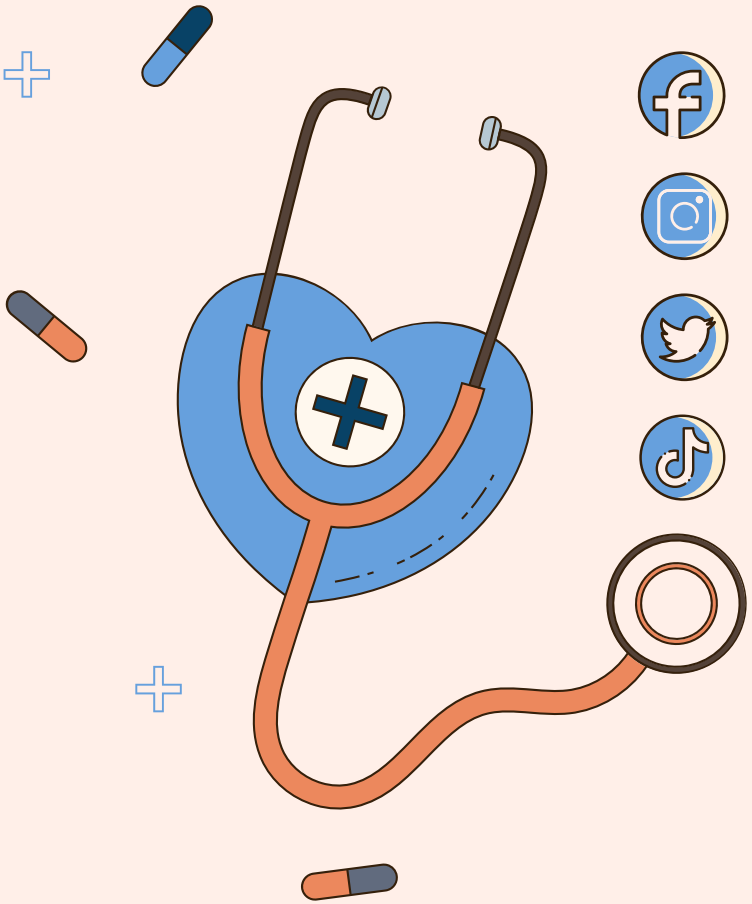
location-specific effects within the V-Blender are the dominant source of product variability

→ Providing clear evidence of non-uniform powder mixing.

CONCLUSIONS

- **Intermediate Dose Thief** is recommended for all future sampling due to its superior precision
- **Process-related issues** are of far greater importance than the choice of instrument
- The primary sources of product variability are a substantial lack of **mixture uniformity** within the V-Blender
- **INTM vs. Tablet:** A systematic loss of approximately 3% of the active ingredient during the powder-to-tablet compression stage





THANKS !

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References

- Cabrera, J., and McDougall, A. (2002) *Statistical Consulting*. Springer-Verlag New York, Inc., ISBN 978-1-4757-3663-2 (eBook).

- Lin, L. I.-K. (1989) A Concordance Correlation Coefficient to Evaluate Reproducibility. *Biometrics*, 45(1), 255--268. DOI: 10.2307/2532051.