



Investigation of API Degradation in Drug Product Stability Study - Correlation of Formulations and Impurity Levels

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Abstract (# W4228)

The prototype formulation T prepared in accordance with the compatibility study showed a major degradant. To determine the degradation pathway of the proposed drug product, different formulations stored at accelerated conditions were prepared to evaluate stability by HPLC method. In the initial impurity testing, the major degradant was 0.10%, 0.20%, 0.14% for formulation R (contained dibasic calcium phosphate, lactose, povidone and sodium starch glycolate), formulation M (included microcrystalline cellulose and starch), and formulation L (contained lactose, povidone and sodium starch glycolate), respectively, then increased to 0.12%, 0.55%, and 0.16% at 60°C oven for two weeks, and 0.42%, 0.92%, 0.51% at 40°C/75% RH for one month. The results indicate that the major excipients of formulation M, microcrystalline cellulose and starch, might be the primary reason for accelerated API degradation in the proposed drug product. Correlations between formulations and impurity levels suggest that the compatibility study could not always predict potential stability problems in the drug product.

Objectives

A drug substance-excipient compatibility study has been used to predict stability problems due to interactions of drug substance with excipients. Previous compatibility studies under the condition of open dish at 40°C/75% RH for 10 days demonstrated that the drug substance (X) has good compatibility with common excipients for oral solid dosage, while API is incompatible with dibasic calcium phosphate (Table 1). However, it was observed that the prototype formulation T prepared in accordance with the compatibility study has a major degradant during the accelerated stability study. Therefore, different formulations were prepared to determine the major degradation pathway of the proposed drug product.

Table 1. Drug-excipient compatibility study. Open dish at 40°C/75% RH for 10 days.

Excipients	Compatible	Incompatible
Microcrystalline Cellulose	x	
Lactose Monohydrate	x	
Pregelatinized Starch	x	
Magnesium Stearate	x	
Dibasic Calcium Phosphate		x
Povidone	x	
Sodium Starch Glycolate	x	

Methods

- Different formulations were prepared as shown in Table 2. Each formulation contains magnesium stearate as lubricant. Formulation R contains dibasic calcium phosphate and lactose as filler/diluent, povidone as binder, and sodium starch glycolate as disintegrant, and formulation L contains only lactose as filler/diluent. Formulation M includes microcrystalline cellulose as filler/disintegrant, and starch as binder. These formulations were packaged as 100 tablets/bottle separately and stored at 40°C/75% RH to evaluate stability.

- At various time points, assay, impurity and dissolution testing were conducted by HPLC method with UV detector at 230nm. A SunFire™ C18 column (4.6 × 250 mm, 5 μm) with 1.0 mL/min flow rate and 10 μL/50 μL injection volume was applied (10 μL for impurity and assay, 50 μL for dissolution).

- Dissolution was performed by USP apparatus I (basket) at 100 rpm in 500 mL de-ionized water at 37°C. At time point of 5, 10, 15, 30, 45 minutes, 10 mL aliquot was taken for HPLC analysis to determine % release of drug substance (X) from each tablet.

Table 2. Formula.

Ingredients	Function	% w/w			
		Formulation T	Formulation M	Formulation R	Formulation L
Drug Substance (X)	API				
Microcrystalline Cellulose	Filler/Disintegrant	28.6%	89.0%		
Lactose Monohydrate	Filler/Diluent	40.0%		45.0%	86.0%
Pregelatinized Starch	Binder	30.0%	10.0%		
Magnesium Stearate	Lubricant	0.8%	0.4%	1.4%	0.4%
Dibasic Calcium Phosphate	Filler/Diluent			40.0%	
Povidone	Binder				5.0%
Sodium Starch Glycolate	Disintegrant				8.0%
Total					100%

Results

1. Stability of Different Formulations

Table 3. Assay of different formulations at 40°C/75%RH. (Specification: 93.0% - 107.0%)

40°C/75%RH	Assay			
	Formulation T	Formulation M	Formulation R	Formulation L
Time 0	103.2%	104.9%	100.0%	99.7%
1 Month	104.2%	103.7%	98.5%	98.2%
2 Month	105.4%	106.2%	101.9%	101.6%
3 Month	103.7%	101.6%	98.2%	97.3%

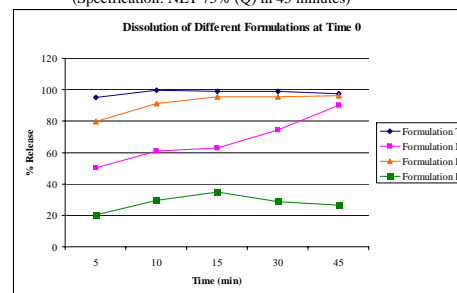
Table 4. Chromatographic purity of different formulations at 40°C/75%RH.

(Specification: Single Known Impurity%_NMT 1.0%,
 Total Unknown Impurities%_NMT 1.0%)

40°C/75%RH	Chromatographic Purity			
	Formulation T	Formulation M	Formulation R	Formulation L
Time 0	0.0%	0.2%	0.1% (TUI%=0.0%)	0.1%
1 Month	0.3%	0.9%	0.4% (TUI%=0.8%)	0.5%
2 Month	1.0%	1.3%	0.6% (TUI%=1.9%)	0.6%
3 Month	2.3%	2.4%	0.6% (TUI%=1.8%)	1.0%

Figure 1. Dissolution of different formulations at time 0.

(Specification: NLT 75% (Q) in 45 minutes)



- Formulation M generates much more impurities than other formulations. Some unknown impurities are detected in formulation R, consistent with the previous compatibility study observations. Formulation L dramatically delays drug release by approximately 70%.

- Comparing these different formulations and results, stability data indicate that hygroscopicity of two major excipients in formulation M, microcrystalline cellulose and starch, might be the main reason to accelerate API degradation in proposed drug product, though they have good drug-excipient compatibility.

2. Stability of Formulation T w/ and w/o Desiccants

Table 5. Assay of formulation T w/ and w/o desiccants at 40°C/75%RH. (Specification: 93.0% - 107.0%)

40°C/75%RH	Assay		
	RLD	Formulation T	Formulation T+Desiccants
Time 0	100.9%	103.2%	102.5%
1 Month		104.2%	102.3%
2 Month		105.4%	102.3%
3 Month		103.7%	101.2%

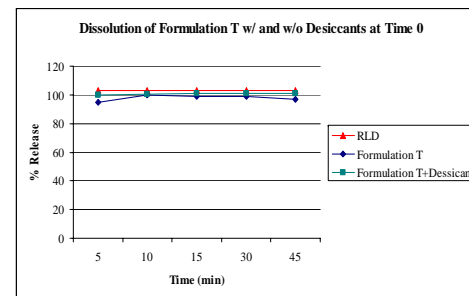
Table 6. Chromatographic purity of formulation T w/ and w/o desiccants at 40°C/75%RH.

(Specification: Single Known Impurity%_NMT 1.0%,
 Total Unknown Impurities%_NMT 1.0%)

40°C/75%RH	Chromatographic Purity		
	RLD	Formulation T	Formulation T+Desiccants
Time 0	0.3%	0.0%	0.1%
1 Month	0.5%	0.3%	0.3%
2 Month	0.7%	1.0%	0.5%
3 Month	0.9%	2.3%	0.7%

Figure 2. Dissolution of formulation T w/ and w/o desiccants at time 0.

(Specification: NLT 75% (Q) in 45 minutes)



Desiccants significantly improve stability of formulation T, supporting our hypothesis that hygroscopicity of microcrystalline cellulose and starch may accelerate API degradation in proposed drug product.

Conclusions

Correlations between formulations and impurity levels suggest that the compatibility study could not always predict potential stability problems in the drug product. Formulations designed to explore drug-excipient interaction in product would optimize formulation development.

References

- ICH Guidelines Q1A (R2) – Stability Testing of New Drug Substances and Products.
- ICH Guidelines Q1E – Evaluation for Stability Data.