Effect of Container Closure Systems on Stability of Pharmaceutical Products

Syngene
Putting Science to Work

Authors: *Sameer S Bhide, Aniruddha Karkal, Chetan Tamhankar*

Abstract:

Syngene is India's largest Contract Research, Development and Manufacturing Organisation catering to over 350 Global clients in Pharma, Biotech, Animal Health, FMCG, Speciality Chemical Industries. Syngene's broad service offering platform enables us to be "One-Stop-Shop" for their discovery and development needs.

In the development services continuum Syngene offers Stability Services to various global clients for Drug substance, Drug Products across various industry segments. Our state-of-the-art Stability Centre has Stability Chambers covering all requirements as per ICH guideline. Our analytical laboratories, fully equipped with all the necessary instruments for characterisation, identification of forms, impurity profiling along with stability testing. All our services are compliant with Current GxP standards.

Syngene's stability centre, specialised in handling stability testing of various dosage forms involving diverse packaging materials, has gathered experience in solving unique problems encountered during stability testing due to packaging material.

Case Study 1: Evaluation of right packaging material

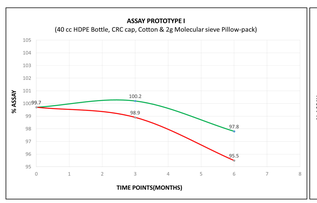
Objective: To evaluate the impact of accelerated (40°C/75% RH), intermediate and long term (25°C/60% RH) stability conditions on description, assay, related substances, dissolution & water content of Prolonged release tablets 8 mg Prototype I & Prototype II packed in HDPE bottle & Alu-Alu blister, the results were compared with RLD which was packed in Blister pack.

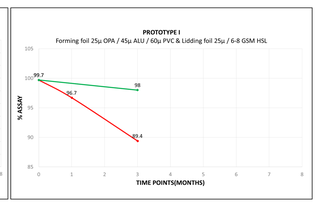
Acceptance Criteria: The acceptance criteria for PR tablets 8 mg Prototype I & Prototype II packed in HDPE bottle & Alu-Alu blister, loaded in accelerated (40°C/75% RH) and long term (25°C/60% RH) stability conditions are as follows:

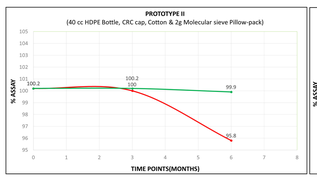
Table showing acceptance criteria for the product.

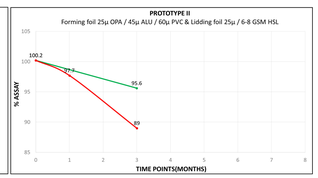
S No.	Test parameter	Acceptance Criteria
1	Assay by HPLC	95.0 to 105.0% of label claim
2	Related substances by HPLC	
	(Imp-A)	NMT 1.00 %
	(Imp-G)	NMT 0.62 %
	(Imp-F)	NMT 0.62 %
	(Imp-B)	NMT 0.62 %
	Any other individual impurity	NMT 0.25%
	Total impurities	NMT 2.00%

Assay Results for Prototype I & II

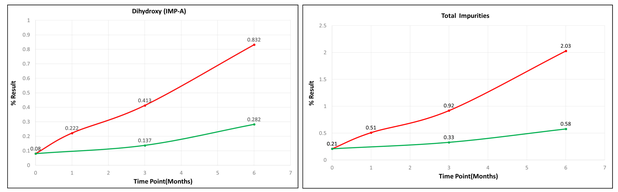




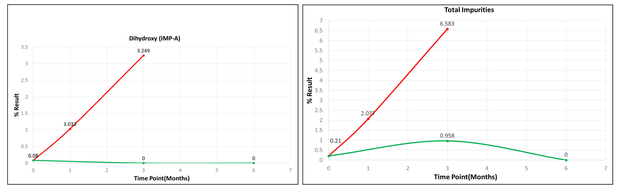




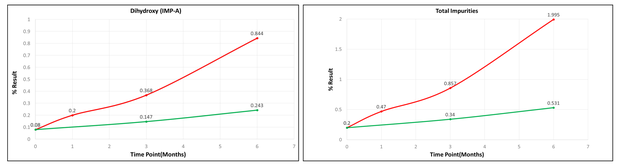
Impurity A & Total Impurity results for Prototype I
(40 cc HDPE Bottle, CRC cap, Cotton & 2g Molecular Sieve Pillow-pack)



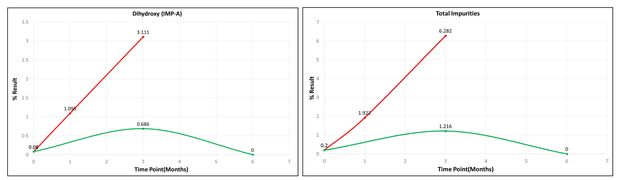
Impurity A & Total Impurity results for Prototype I
Forming foil 25µ OPA/45µ ALU/60µ PVC & Lidding foil 25µ/6-8 GSM



Impurity A & Total Impurity results for Prototype II
(40 cc HDPE Bottle, CRC cap, Cotton & 2g Molecular Sieve Pillow-pack)



Impurity A & Total Impurity results for Prototype II
Forming foil 25µ OPA/45µ ALU/60µ PVC & Lidding foil 25µ/6-8 GSM



Observation

- No significant change in description, water content and dissolution profile was observed at accelerated, and real time condition of both the prototypes packed in HDPE bottle and Alu-Alu blister. All the stability samples were found to meet the desired acceptance criteria.
- Increase in impurity profile was observed at accelerated condition in both HDPE bottle and Alu-Alu blister pack configurations, On the basis of observations, the recommended storage condition i.e. ***Do not store above 25 °C.***
- There was no significant increase in impurity profile of both the prototypes at real time condition especially in HDPE bottle pack when compared to Alu-Alu blister pack.
- There was a significant increase of impurity profile at accelerated condition in Alu-Alu blister pack when compared to HDPE bottles.

Conclusion

- As evident from the above stability results, both the Pilot BE Prototypes were found to have similar trend in all stability conditions & packs evaluated.
- Based on the real time stability trend,**HDPE bottle pack** (40 cc HDPE Bottle, CRC cap, Cotton & 2g Molecular Sieve Pillow-pack) seems to be the preferred pack configuration when compared to Alu-Alu blister.
- Both the Prototypes packed in HDPE bottle are deemed to be stable as per the recommended storage condition.

Case Study 2: Impact of packaging material on product

Objective: To evaluate the impact of accelerated (40°C/75% RH) and long term (25°C/60% RH) stability conditions on description, assay, related substances, dissolution & water content of Prolonged release tablets X Mg Prototype I packed in HDPE bottle & labelled. The evaluation during the course of study resulted in an abnormal behavior wherein the impurity was found to decrease at accelerated condition and gradually increase with ageing at Long term condition.

Table showing product information

Name of the Product	Prolonged Release Tablet 8 mg		
Objective/ Remark	To perform informal stability study of Prolonged Release Tablets 8 mg (Prototype I)		
Batch No.	**XYZ**	**Batch Mfg. Date:** 27 Jun 18	
Batch size	X kg		
Protocol No.	**XYZ**	**Study Start Date**	17 Jul 2018
API		**API Batch No.**	
Pack Count	30 tablets per bottle	**Location**	
Packaging	40 cc HDPE Bottle, CRC cap, Cotton & 2g Molecular sieve Pillow-pack		

Test	**Description, Assay, Related Substances, Dissolution and Water content**					
Pack Configuration	**Storage Conditions**	**1 Month**	**3 Months**	**6 Months**	**12 Months**	**Reserve**
HDPE Bottle (1 Bottle contains 30 tablets)	**40°C ± 2°C/75% ± 5% RH**	√ (2 Bottles)	√ (2 Bottles)	√ (2 Bottles)	-	-
	25°C ± 2°C/60% ± 5% RH	-	√ (2 Bottles)	√ (2 Bottles)	√ (2 Bottles)	√ (2 Bottles)
Date Out		**17 Aug 2018**	**17 Oct 2018**	**17 Jan 2019**	17 Jul 2019	NA

Table showing acceptance criteria

S No.	Test parameter	Acceptance Criteria
1	Assay by HPLC	95.0 to 105.0% of label claim
2	Related substances by HPLC	
	(Imp-A)	NMT 1.00 %
	(Imp-B)	NMT 0.62 %
	Any other individual impurity	NMT 0.25%
	Total impurities	NMT 2.00%

Overlay of 1 Month, 3 Month, 6 Month_40°C/75% RH_40 cc HDPE Bottle, CRC cap, Cotton & 2g Molecular sieve Pillow-pack

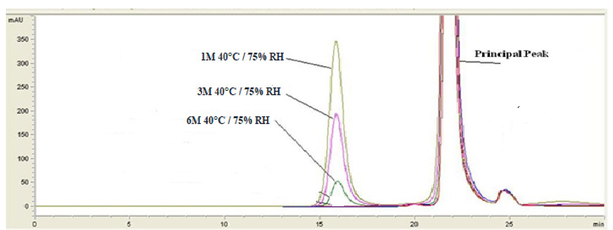


Table showing stability data of 30 count HDPE bottle pack.

Batch No.	**XYZ**											
Condition	**Initial**		**1M 40°C/ 75% RH**		**3M 40°C/ 75% RH**		**6M 40°C/ 75% RH**		**3M 25°C/ 60% RH**		**6M 25°C/ 60% RH**	
Pack Configuration			**40 cc HDPE Bottle, CRC cap, Cotton & 2g Molecular sieve Pillow-pack**									
Assay by HPLC	99.70%		97.62%		98.90%		95.50%		100.20%		97.80%	
Water by KF	2.20%		2.29%		2.29%		2.95%		2.40%		2.78%	
Related Substances												
Impurity Name	**RRT**	**%**	**RRT**	**%**	**RRT**	**%**	**RRT**	**%**	**RRT**	**%**	**RRT**	**%**
(IMP-A)	-	0.08	0.27	0.222	0.27	0.413	0.27	0.832	0.27	0.137	0.26	0.282
(IMP-B)	-	0.05	0.33	0.080	0.32	0.092	0.32	0.109	0.34	0.067	0.31	0.088
Unknown Impurity-1	-	-	0.72	0.924	0.73	0.622	0.72	0.412	0.72	0.12	0.72	0.18
Highest Unknown	-	**ND**	-	**0.924**	-	**0.622**	-	**0.412**	-	**0.12**	-	**0.18**
Total Impurities		**0.21**		**1.43**		**1.47**		**1.82**		**0.448**		**0.58**

Observation

- No significant change in description and dissolution profile was observed at accelerated and real time condition in HDPE bottle. All the stability samples were found to meet the desired acceptance criteria.
- The impurity profile showed a dramatically reverse characteristics i.e a decrease in % at 40/75 condition with aging while it showed a gradual increase in % impurity at the same retention time at 25/60 with aging.

Conclusion

- On a thorough investigation and LC-MS analysis it was observed that the impurity was not a degradant of the API but was due to permeation of the component of Lacquer adhesive which permeated at high temperature and was detected as unknown impurity. This over a period of time degraded further and could not be detected as the further degradant was having no absorbance at the wavelength used for analysis. While at Long term condition the impurity was found to gradually increase over time.

  Syngene recommended client to use different quality label. Stability samples analyzed after implementation of the recommendation did not show any unknown impurity peaks.

Executive Summary:

1. Our broad offering platform enables us to be a "one-stop-shop" for your discovery and development needs...
2. Our State of Art Stability center is Asia's biggest infrastructure catering to some of the TOP Ten pharma clients.
3. The Stability centre is being Audited by number of Regulatory agencies and is experienced in Handling the early phase till commercial stability.
4. We solve complex R&D problems for our clients by providing data ready for regulatory submission and with inputs towards packaging of the product to maximise stability.
5. With a highly experienced and qualified team of scientists we reduce the time from laboratory to Market.
6. We continue to invest in state-of-the-art infrastructure with due focus on people capabilities, compliant systems & processes.