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Original Article

ICH Q1 a Stability Testing for New Dosage Form

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ABSTRACT

Background: This study presents a comprehensive study on applying the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q1A R2 guideline for conducting stability tests on new drug substances and products. **Materials and Methods:** This study focused on the stability of multivitamin syrup under specific storage conditions, following ICH guidelines. The syrup was subjected to various tests, including pH measurement, weight per mL determination, microbial limit testing and assay analysis. Along with OOS, OOT and root cause analysis. **Results:** Showed that the syrup maintained its yellow color, met pH specifications and had the appropriate weight per mL. Microbial limit tests revealed no presence of harmful bacteria and assay analysis confirmed the purity and quantity of the components in the syrup. A survey on tablet preparations also demonstrated stability and quality. **Conclusion:** Overall, the stability studies indicated that the multivitamin syrup met all specifications and was considered stable. These findings contribute to ensuring the safety and effectiveness of the product throughout its shelf life.

Keywords: ICH Q1A R2, Stability test, Shelf life, Storage conditions, Storage durations.

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INTRODUCTION

"The ability of a drug substance or drug product to remain within specifications established to ensure its identity, strength, quality and purity throughout the retest or expiration dating period" is the definition of stability in the context of pharmaceutical products.[1] Drug instability may result in an undesirable change in performance that results in the failure of the product. Every pharmaceutical product must have an expiration date as it represents a critical quality parameter. Ideally, alongside the expiration date, there should also be guidance on the recommended storage conditions.[2]

Stability studies are one of the most crucial steps in the creation of a pharmaceutical since they ensure the identity, potency and purity of both the raw materials and the finished goods.[3] After it has been produced, a pharmaceutical product's stability is influenced by a number of environmental factors, such as the ambient temperature, humidity and light levels, as well as factors unique to the product, such as the chemical and physical properties of the active ingredients and pharmaceutical excipients, the composition of the dosage form, the manufacturing process, the type of container closure system and the characteristics of the packing material.[4-6] Stability studies are an integral part of the drug development process, which consists of six distinct phases namely Stage 1, Stage 2, Stage 3, Stage 4, Stage 5, Stage 6.[7] The objective of performing stability testing is to establish shelf-life and processing specifications for new products, to investigate whether the breakdown of active medications may result in the formation of toxic compounds, to ensure that the brand is fit for usage for the duration that it is on the market and has all functionally acceptable features to preserve the manufacturer's good name.[8-14] The stability studies are also done to check if any deviation have been made during the manufacturing process or formulation process which might lead to detrimental effects on product stability. Stability studies provide valuable insights in selecting excipients, formulations and container-closing techniques. More importantly, stability studies are the only method to definitively determine whether

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or not a pharmaceutical drug fulfills the criteria for approval. According to various studies and investigations there are many factors which will affect drug stability. The drug stability is influenced by many such factors are temperature[15-17] moisture, pH, excipients, Oxygen, light, etc. Apart from the mentioned factors, there are also factors such as physical stability,[18] chemical stability, microbiological stability and therapeutic stability of the drug substances.

Stability testing is a customary approach applied throughout the diverse phases of pharmaceutical substance and product development. In the initial stages, accelerated stability tests are employed to evaluate the type of degradation observed after prolonged storage. The primary objectives of pharmaceutical stability testing are to ensure that products remain suitable for consumption until the final pharmaceutical unit is used and that they maintain their acceptable quality throughout their market presence.[19] There are four categories of stability testing methodologies widely employed namely real-time stability testing, accelerated stability testing, retained sample stability testing and cyclic temperature stress testing. The Real-time stability test Utilizes trend analysis, relevant data is collected at an appropriate frequency to distinguish instability from everyday fluctuations throughout the testing process.[20] Accelerated stability testing exposes a product to higher temperatures and various stress factors to determine heat-induced failure. Stressors like humidity, heat, turbulence, weight, pH and packaging are applied and samples are stretched, cooled and then analysed quickly to reduce measurement instability compared to real-time testing. For thermo-labile and protein components, reliable stability predictions require avoiding denaturing stress temperatures. Four different stress levels are recommended for statistical validity.[21,22] The Arrhenius equation is used to forecast stability based on degradation rates at high temperatures and it can predict degradation under "stress" at lower temperatures.[23] According to Retained sample stability testing, it is customary to test samples at predefined intervals for stability if a product has a shelf life of five years, therefore stability samples are examined at 3, 6, 9, 12, 18, 24, 36, 48 and 60 months. The constant interval procedures are the accepted method for gathering stability data on samples that have been stored.[24] Cyclic stress testing primarily emphasises aspects such as stability, potency, purity and formulation, as opposed to physical stressors such as temperature cycling.

Stability chambers are environmental specialist chambers that can stimulate storage conditions and real-time stability, expedited stability and protocol for the long term. They are used for stability testing and allow for the evaluation of product stability. There are 2 different kinds of light sources employed in the photostability chamber such as cool white and near UV fluorescent tubes are combined and daylight artificial lamps (e.g., metal halide or xenon). A maximum exposure of 1.2 million lux hours is required. A lux metre is used to determine the amount of visible light necessary and the number of hours of exposure.[25]

Stability Climate zone testing was done using regional average annual temperature and relative humidity.[25] The structured approach within the drug development process is stability testing. Stability data for the pharmaceutical compound play a crucial role in determining suitable storage conditions and packaging for large quantities of the substance.[26] The goal of conducting stability studies on the drug product is to determine its shelf life or expiration date.[27-29]

MATERIALS AND METHODS

Stability studies for new drug dosage form of syrup

pH

Connect the pH meter to a power source and allow it to warm up for duration of 5 to 10 min. Switch it to pH mode when you're ready to record the pH values.

The weight per millilitre

Weight per milliliter (weight per mL) of a liquid refers to the weight in grams of 1 mL of the liquid at 20°C unless specified otherwise. This method is employed in tests for oral solutions and suspensions. To calculate the weight per milliliter (g per mL) for content determination, a known quantity of the solution or suspension is weighed and its weight per mL is obtained by dividing the weight of the liquid filling a specific pycnometer at the specified temperature by the pycnometer's capacity in milliliters at that temperature. The pycnometer's capacity is determined by measuring the weight of water required to fill it at that temperature.

Microbial count

Media

The following products are sourced from Topley House at 52 Wash Lane, Bury, Lancashire, UK, BL96AS: Nutrient broth, nutrient agar, Mac Conkey agar, Mannitol salt agar, Cetrimide agar, Mueller-Hinton agar, Salmonella-Shigella agar and Saboraud Dextrose agar.

For the preparation of tablet dispersion

Two tablets from each blister-packed paracetamol, brand were placed in 10 mL of sterile normal saline, mixed for 5 min using a vortex mixer to dislodge microbes and the liquid above settled solid particles (supernatant) was used for further analysis.

To assess the microbiological quality of the tablets

1 mL from each brand's dispersion was plated on duplicate nutrient agar plates. This process was repeated with MacConkey agar, Mannitol salt agar, cetrimide agar, Salmonella-Shigella agar

and Saboraud Dextrose agar. Saboraud Dextrose agar plates were incubated at 25°C for 72-96 hr, while the others were incubated at 37°C for 48 hr. After incubation, plates were inspected for microbial growth.

Determination of microbiological quality of syrups

Multivitamin syrup was diluted in sterile peptone water at ratios of 1:10, 1:100 and 1:1000. Each dilution (0.1 mL) was inoculated onto duplicate Petri dishes with various agar media. These plates were incubated at 37°C for 24-48 hr, except for Saboraud Dextrose agar, which was incubated at 25°C for 72-96 hr. After incubation, plates were checked for microbial growth. Bacterial isolates from growth-positive plates underwent standard microbiological identification tests to confirm their identity and purity, including colony morphology assessment and conventional biochemical tests.

Antibiotic susceptibility profiling

The antibiotic susceptibility testing, both Gram-negative and Gram-positive isolates were assessed using the disc diffusion method, following Clinical and Laboratory Standards Institute (CLSI) guidelines. Gram-negative bacteria were tested against eight antibiotics, including augmentin (30 µg), ofloxacin (5 µg), gentamycin (10 µg), nalidixic acid (30 µg), nitrofurantoin (200 µg), cotrimoxazole (25 µg), amoxycillin (25 µg) and tetracycline (25 µg). Gram-positive bacteria were tested against three antibiotics, which were oxacillin (1 µg), cefuroxime (30 µg) and vancomycin (30 µg).

To perform the susceptibility tests, colonies from a nutrient agar plate were suspended in sterile distilled water and adjusted to a turbidity equivalent to a 0.5 McFarland standard. This suspension was spread onto Mueller Hinton agar plates and allowed to acclimatize and grow at 37°C for 20 min. Antibiotic discs were placed on the agar surface and refrigerated for 30 min for proper diffusion. A control strain, *E. coli* ATCC 25922, was used as a reference. After 18 hr of incubation at 37°C, the diameters of inhibition zones were measured in millimeters and interpreted according to CLSI guidelines.

Assay by USP 2010 Official method

Preparation of mobile phase

A 1000 mL volumetric flask was filled with 4.4 g of dibasic potassium phosphate and 500 mg of sodium 1-octanesulfonate and the mixture was then diluted with water to volume. A pH of 8.20 0.05 was achieved by adding phosphoric acid to the mixture. Then, the 45:40:15 mixtures of acetonitrile, octane sulfonate buffer and methanol was filtered and degassed to create the mobile phase.

Preparation of diluent A

Initially, 1.7 g of monobasic ammonium phosphate were placed into a 1 L volumetric flask and subsequently filled with water to reach the desired volume. The pH was then meticulously adjusted to 10.00±0.05 using ammonium hydroxide. Subsequently, a diluent labeled as "A" was formulated by combining ammonium phosphate buffer (pH 10), methanol and acetonitrile in a precise ratio of 35:35:30.

Preparation of standard azithromycin solution

Initially, a standard azithromycin solution was created by placing 20 mg of USP azithromycin RS into a 50 mL volumetric flask. Diluent A was then introduced to reach the flask's calibration mark, followed by sonication to achieve a solution with a concentration of 0.4 mg of azithromycin per milliliter.

Preparation of sample solution

The multivitamin syrup was taken. This was mixed with 75 mL of Diluent A, sonicated for 15 min and diluted to the flask's mark. From this solution, 6.0 mL were transferred to a 50 mL flask, further diluted with Diluent A to reach a 0.4 mg/mL syrup concentration and filtered through a 0.45 µm filter. The chromatographic system used a liquid chromatograph with a 210-nm detector, a 4.6 mm × 25 cm column with 5-mm L1 packing and operated at a flow rate of 1.5 mL/min for a total run time of 30 min. The column was consistently maintained at 50°C and HPLC was executed, verifying column equilibrium with a standard solution (50 µL) until the relative standard deviation stayed below 2% for six consecutive injections.

Assay procedure

In equal quantities, approximately 50 µL of the multivitamin syrup,[30] were independently introduced into the chromatograph. The peak area responses (n=3) were recorded for all peaks. Subsequently, the percentage content of azithromycin was determined using the following formula:

$$\% \text{ Content} = (\text{Peak area of sample} / \text{Peak area of standard}) \times 100$$

Stability of pharmaceutical preparations listed in the ICH Model

Survey was conducted based on the parameters which are given in Table 4 following results.

OOS (Out of Specification)

This is performed to assess and address instances where a product or sample does not meet established specifications or quality standards. This test is done to check if any deviating from the defined parameters of a product and if any findings suggest any deviation it is labeled as an "OOS" result, OOS causes can be categorized as Assignable (when the cause of the error is identified) and Non-assignable (When the cause of the error

remains unidentified).These determinations are communicated by the Quality Control (QC) team to designated personnel responsible for OOS classification, distinguishing between assignable and non-assignable causes.

OOT (Out of Trend)

An analytical result that whilst being in the specification, falls outside of the expected normal or pre-defined for that test parameter. This shall be identified during analysis by comparing against trend and results obtained at the extreme of specification. In general, Out of Trend can be described as a result of sequence of results that are within specification limits but are unexpected and not in line with the routine.

Hypothesis/Investigative Testing

It refers to testing that is carried out to either substantiate or rule out potential root causes based on initial assumptions. This involves conducting additional tests to investigate what could have occurred, which can encompass various aspects such as further testing related to sample filtration, sonication/extraction, or potential equipment malfunctions, among others. This process allows for the exploration of multiple hypotheses.

RESULTS

Stability studies for new drug product

The test was conducted on the stability of multivitamin syrup under storage conditions at a temperature of 300°C±20°C/ relative humidity 65%±5% with a test duration of 6 months according to ICH guidelines. The production batch size of the product is 1000 L. The test started on 05/10/2022 and ended on 04/09/2024, as shown in Table 1.

According to the specifications, the syrup was found to be yellow-colored syrup contained in a duly graded amber-colored PET bottle with a yellow metallic cap. In the 1st month, 3rd month and 6th month, the targets specified in Table 1 are met.

The specification of the drug product pH is 3.0-4.5. 1st month it was found to be 4.02. In 3rd month pH was found to be 4.01 and 6th month, the pH was found to be 4.0. The pH of the product compiles the specifications in Table 1.

The product specification of the weight for mL is 1.00 to 1.15 g/ mL. In the 1st month, the result was found to be 1.1020 g/mL. In the 3rd month, the result was found to be 1.1018 g/mL and in the 6th month, the result was found to be 1.1019 g/mL. The weight per mL of the product compiles the specification. The date of analysis of the above tests is as per specifications shown in Table 1.

Microbial limit test

The specification of Total yeast and mold count is not more than 100 cfu/mL and not less than 10 cfu/mL. The first month it was found to be 25 cfu/mL and less than 10 cfu/mL. The 3rd month it was found to be 25 cfu/mL and less than 10 cfu/mL and 6th month it was found to be 30 cfu/mL and less than 10 cfu/mL as shown in Table 2.

The specification of *Escherichia coli* should be absent. In the 1st, 3rd and 6th months, there were no *Escherichia coli* was present.

The specification of *Salmonella* should be absent. In the 1st, 3rd and 6th months, there were no *Salmonella* present.

The specification of *Pseudomonas aeruginosa* should be absent. In the 1st, 3rd and 6th months there were no *Pseudomonas aeruginosa* was present.

The specification of *Staphylococcus aureus* should be absent. In the 1st, 3rd and 6th months, there were no *Staphylococcus aureus* was present.

The results of microbial limit studies of the product were found as per ICH specification. This means the product is stable.

Assay

We conducted purity and quantity tests on syrup, following ICH specifications (not less than 90% purity). Here are the results for each component shown in Table 3.

Thiamine Hydrochloride BP: 1st month:3.2012 mg (160.06%), 3rd month: 3.1982 mg (159.91%).

6th month: 3.1892 mg (159.46%).

Riboflavin Sodium Phosphate BP: 1st month: 3.9984 mg (157.42%), 3rd month: 3.9910 mg (157.13%), 6th month: 3.9674 mg (156.20%).

Pyridoxine Hydrochloride BP: 1st month: 3.2984 mg (164.92%), 3rd month: 3.2965 mg (164.83%), 6th month: 3.2940 mg (164.70%).

Niacinamide BP: 1st month: 21.3300 mg (106.65%), 3rd month: 21.3285 mg (106.64%), 6th month: 21.3225 mg (106.61%).

D-Panthenol BP: 1st month: 6.5855 mg (109.76%), 3rd month: 6.5827mg (109.71%),

6th month: 6.5778 mg (109.63%).

Ascorbic Acid BP: 1st month: 100.2912 mg (133.72%), 3rd month: 100.2619 mg (133.68%),

6th month: 100.2022 mg (133.60%).

All components met or exceeded the required 90% purity level.

Survey on the stability of pharmaceutical preparations

We surveyed pharmaceutical tablet preparations manufactured by the production department. The syrup was stored at 30°C±20°C/RH 65%±5% for 6 months using blister packaging as the primary packaging. No color or physical changes occurred in the packaging material over this period. The assay showed 90%

Table 1: Multivitamin syrup details and description for Stabiliy Studies.

Generic name	Multivitamin syrup		MFG Date		10/2022	
Batch no. Smsd0101			Exp date		09/2024	
			Test started on		05/10/2022	
Batch size	1000 Ltr.		Test completed on		04/05/2023	
Storage conditions	Temp 30^{0}C±2^{0}C / RH 65 %±5%					
Format no.	F/14/00/QC/020	REF. SOP NO.	QC/020	EFFECTIVE DATE	28/04/2023	
Description, pH, Weight per mL test report						
Test	**Specification**	**Initial**	**After 3 Months**	**After 6 months**		
Description	Yellow color syrup filled in amber color PET bottle duly sealed with a golden color metallic cap.	Complies	Complies	Complies		
pH	3.0 to 4.5	4.02	4.01	4.00		
Weight per mL	1.00 to 1.15 g/mL	1.1020	1.1018	1.1019		

Table 2: Microbial test results.

Microbial Limit test				
Test	**Specification**	**Initial**	**After 3 Months**	**After 6 months**
Total viable count Total Yeast and Mould Count	NMT 100 cfu/mL Less than 10 cfu/mL.	25 cfu/mL <10 cfu/mL	25 cfu/mL <10 cfu/mL	30 cfu/mL <10 cfu/mL
Escherichia coli	Should be absent.	Absent	Absent	Absent
Salmonellae	Should be absent.	Absent	Absent	Absent
Pseudomonas aeruginosa	Should be absent.	Absent	Absent	Absent
Staphylococcus aureus	Should be absent.	Absent	Absent	Absent

Table 3: Assay test results of multivitamin syrup.

Test		Specification	Initial	After 3 Months	After 6 months
Assay: Each 5 mL Contains:	Thiamine Hydrochloride BP 2 mg.	NLT 90%	3.2012 mg (160.06%)	3.1982 mg (159.91%)	3.1892 mg (159.46%)
	Riboflavin Sodium Phosphate BP 2.54 mg.	NLT 90%	3.9984 mg (157.42%)	3.9910 mg (157.13%)	3.9674 mg (156.20%)
	Pyridoxine Hydrochloride BP 2 mg.	NLT 90%	3.2984 mg (164.92%)	3.2965 mg (164.83%)	3.2940 mg (164.70%)
	Niacinamide BP 20 mg.	NLT 90%	21.3300 mg (106.65%)	21.3285 mg (106.64%)	21.3225 mg (106.61%)
	D-Panthenol BP 6 mg.	NLT 90%	6.5855 mg (109.76%)	6.5827 mg (109.71%)	6.5778 mg (109.63) %
	Ascorbic Acid BP 75 mg.	NLT 90%	100.2912 mg (133.72%)	100.2619 mg (133.68%)	100.2022mg (133.60%)

drug content, with no color or physical changes in the tablets. Microbial studies found no bacteria, fungi, or pyrogens.

OOS (Out of Specification)

The product was found to be in the specification as there is no Assignable (when the cause of the error is identified) and Non-assignable (When the cause of the error remains unidentified) errors observed in the syrup this proves that the syrup meets all the requirements as per specification in the guideline.

As shown in Table 4 the product meets all specifications and is considered stable. The same formulation of syrup with different batches also showed stability under the same storage conditions, with no color or physical changes, compliance in identification and purity tests and no microbial contamination. The OOT Test

Table 4: OOS desription of Multivitamin syrup.

B Date of OOT occurrence :05/04/2023		OOT Reference No.: QA/OOT/01	
OOT REPORTING: *(To be completed by analyst)*			
Product/ Material Name	Multivitamin Syrup	QC Reference No.	QC/OOT/02
Batch No.	SMSD0102	Mfg. Date	10/2022
Specification No.	02	Expiry Date	09/2024
Test Name	Finish process quality control test	Test Method No.	01
Stage of testing (For Drug substance/ Intermediate / Drug product) *(select)*	In-process. Finished product/Intermediate release testing. Stability 6 Months Accelerated/Long Term/Intermediate.		
Summary of OOT Test Results *(state result and specification).*			
There were no color changes or physical changes with the product. In the identification test and the purity test, it compiles the specification. In the case of microbial studies, there were no microorganisms such as bacteria, fungi, or pyrogens found. The product is stable and the product compiles all the specification.			
Details of abnormal observations noted during the testing, if any			
No abnormal observations noted during the testing. The drug formulations meet well within the specification.			

Results of the syrup No abnormal observations noted during the testing. The formulations meet well within the specification and hence root causes analysis was ruled out in Hypothesis/ Investigative Testing.

DISCUSSION

The stability studies conducted on the multivitamin syrup showed positive results, indicating that the product is stable under the specified storage conditions. The syrup maintained its yellow color and met the specified targets throughout the 6-month test period. The pH of the product also complied with the specifications, remaining within the range of 3.0 to 4.5.

The weight per mL of the syrup was within the specified range of 1.00 to 1.15 g/mL, demonstrating that the product met the weight specification. Microbial limit tests were conducted to assess the presence of microorganisms in the syrup. The results showed that the total yeast and mold count remained below the maximum limit of 100 cfu/mL and above the minimum limit of 10 cfu/mL throughout the test period. Additionally, no *Escherichia coli, Salmonella, Pseudomonas aeruginosa*, or *Staphylococcus aureus* were detected in any of the monthly tests, indicating that the product was free from these harmful bacteria.

Assay tests were performed to determine the purity and quantity of the components in the syrup. All components, including Thiamine Hydrochloride BP, Riboflavin Sodium Phosphate BP, Pyridoxine Hydrochloride BP, Niacinamide BP, D-Panthenol BP and Ascorbic Acid BP, met or exceeded the required 90% purity level. This indicates that the syrup contained the specified amounts of each component and was of high quality.

A survey was also conducted on multivitamin syrup preparations manufactured by the production department. The syrup showed no color or physical changes in the packaging material. The assay tests on the syrup revealed a 90% drug content and microbial studies found no presence of bacteria, fungi, or pyrogens. This further confirms the stability and quality of the product.

Overall, the stability studies, microbial limit tests and assay tests demonstrate that the multivitamin syrup meets all specifications and is considered stable. The consistent results obtained from different batches of the syrup further support its stability and quality. No out-of-specification errors were observed, indicating that the product meets all requirements as per the guidelines.

CONCLUSION

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ICH: International Council for Harmonisation; **OOT:** Out-of-trend; **RH:** Relative humidity; **GMP:** Good manufacturing practice; **Cfu:** Colony forming units; **OOS:** Out of Specification; **CLSI:** Clinical and Laboratory Standards Institute.

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