International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

Use Of Microbiology In Stability Testing For Sterile Paracetamol Solution For Infusion 1000mg /100 Ml & Its Method Validation Of Non-Sterile And Sterile Sample

Fariya Banu[1], Mrs. Khadijah Al Khadir[2], Abdur Rafay Muzzamil[3]
[1]PG Student, Department of Microbiology, Mumtaz Degree and PG College. Hyderabad, India.
[2]Head, Department of Microbiology, Mumtaz Degree and PG College. Hyderabad, India.
[3]Director, NSQ Pharma Pvt Ltd, Hyderabad, India.

Accepted 23rd May 2025

ABSTRACT
The stability studies of pharmaceutical products are one of the very, important parameter for development of new drugs as well as new, formulations. The shelf-life prediction is a major role for the, pharmaceutical product development of all the dosage forms and also it, is utilized to determine the particular storage conditions and to suggest, label instructions. Stability studies of pharmaceutical products ensuring, the maintenance of product quality, safety and efficacy throughout the, shelf life are considered as pre-requisite for the acceptance and, approval of any pharmaceutical products. This review gives a brief overview about microbial contamination in pharmaceutical products. We discuss the distribution and potential sources of microorganisms in different areas, ranging from manufacturing sites, pharmacy stores, hospitals, to the post-market phase. We also discuss the factors that affect microbial contamination in popular dosage forms (e.g., ***sterile PARACETAMOL SOLUTION FOR INFUSION 1000MG /100 Ml****). When these products are contaminated, the microorganisms can cause changes. The effects range from mild changes (e.g., discoloration, turbid type) to severe effects (e.g., changes in activities, toxicity). The most common method for countering microbial contamination is the use of preservatives. These studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO or other agencies Bioburden is measure of microbial contamination or microbial load; the amount of microorganisms contaminating an object. Each lot of a component, drug product container, or closure with potential for microbiological contamination that is frightful in perspective of its planned utilize might be subjected to microbiological tests before utilize*
Sterility testing is a critical quality control procedure used to ensure that pharmaceutical products, medical devices, and biological preparations are free from viable contaminating microorganisms such as bacteria, fungi, and yeast. The test is particularly important for products that are required to be sterile, including injectable medications, intravenous fluids, ophthalmic preparations, and implantable devices. The main objective of sterility testing is to confirm the absence of microbial contamination in the final product, which could lead to serious infections or adverse reactions in patients. The testing process is typically performed using two main methods: membrane filtration and direct inoculation. In membrane filtration, the product is passed through a sterile filter that traps any microorganisms, which are then incubated in a growth medium and monitored for microbial growth over a specified period, usually 14 days.

INTRODUCTION

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the roduct can be defined as the substance reduces to 90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparations. The expiry of the pharmaceutical dosage form depends on various environmental factors such as temperature, humidity, light, radiations etc. and many physical and chemical active substances in the formulation, the nature of container-closures used and the storage conditions. Literature data on the decomposition process and degradability of active substances are generally available together with adequate analytical methods Microbiological stability testing is a crucial component of the pharmaceutical development process, particularly for products that are intended for parenteral use, ophthalmic applications, or other routes where sterility is essential. This testing evaluates how a product's microbiological quality is maintained over time under various storage conditions. By assessing the effectiveness of preservatives and the potential for microbial growth, manufacturers can ensure that their products remain safe and effective throughout their shelf life. *Microbiological stability testing* is especially important for formulations like injectables, eye drops, and creams that are exposed

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

to external contaminants or may be susceptible to microbial growth during storage. In this we will provide a comprehensive guide to conducting *microbiological stability testing*, explaining its importance, the methods used, and best practices to ensure accurate and reliable results. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation.

IMPORTANCE OF STABILITY STUDIES

1) Product instability of active drug may lead to under medication due to the lowering of the drug in dosage form.
2) During the decomposition of the drug or product it may lead to toxic products.
3) During the marketing from one place to another during the transportation the drug has the compatibility to change its physical properties.
4) Instability may be due to changing in physical appearance through the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study.

TYPES OF STABILITY STUDIES ON DRUG SUBSTANCES

A comprehensive pharmacopeial protocol (USP) prescribes the criteria for acceptable levels of physical, chemical, microbiological, therapeutic and toxicological stability studies.

Physical stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate,hence it is important for the efficacy and safety of the product.

Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product.

Types of stability studies

Stability studies are used for testing the drug product for longer periods under varying conditions of temperature and Relative Humidity (RH). If the drug is to be distributed in different geographical regions and if shipping is required for transportation, in that case long term stability studies are of prime importance. Long term stability studies are performed by testing the sample at specific time intervals and conditions of external parameters are changed accordingly. Main objective of this study is to determine shelf-life of the drug product. Stability studies are mainly four types, they are Long term stability, Intermediate stability, Accelerated stability and In-use stability Studies. The type of stability studies and its storage conditions with respective time period were shown in below Table.

Types of Stability Studies	**Storage Conditions**	**Minimum Time Period (Months)**
Long Term (real time)	25±2°C and 60±5% RH or 30±2°C and 65±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. In the early stages, the stability testing is performed by the accelerated stability studies which mainly are performed at high temperature\ humidity. The accelerated stability studies is easy to predict the degradation of the drug within short period of time. In the accelerated stability studies mainly the drug is performed at long-term storage. During this elevated temperatures are used to determine the products shelf-life. The main aim for the stability testing is to provide the acceptance level of fitness/ quality throughout the period during which they are available for the patience and should be fit for the acceptance of the drug by the patient. This helps the patient to be cured easily and the acceptance of the drug would be easy and the known therapeutic uses of the pharmaceutical products manufactured. Depending upon the aim, steps followed, the stability testing

procedures have been categorized into four types and they are

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

Real-time stability testing

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time from inter-assay variation. While, testing the samples are collected at regular intervals such that the data is collected at the appropriate frequency such that the analyst is able to distinguish the degradation day-to-day. The data can be increased by including the single batch of reference material for which stability characteristics have been established. In this the reagents and the instruments used should be in the consistency throughout the stability testing. The control of drift and discontinuity results in the changes of both reagents and instruments should be monitored

Accelerated stability testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations. The accelerated stability studies is easy to predict the shelf life thus reduces the duration to know the stability of the substance. In addition to temperature, stress conditions are applied such as moisture, light, pH and gravity. Due to the measurement of instability time is also reduced in comparison to the real-time testing. For the accelerated stability studies the stability projections are done at four different stress temperatures. However, projections are obtained when denaturing stress temperatures are avoided. The accelerated stability studies are easily predicted by the Arrhenius equation

$$K = Ae\text{-}Ea/RT$$

GUIDANCE OF STABILITY STUDIES

The drug to be administered for wellbeing of the patient the pharmaceutical preparation should be optimally stable and products are manufactured according to the standard guidance which are proposed by WHO, FDA, ICH. ICH plays a key role in the preparation and marketing of the preparations. ICH stands for "International Conference of Harmonization" which is used for the register of the pharmaceutical's products for human use. The ICH was established in 1991, was a consortium formed inputs from both regulatory and industry from European commission, Japan, USA and various guidelines for drug substance and drug product came into existence regarding their quality, safety, efficacy and multidisciplinary (also known as Q, S, E, M). The secretariat of ICH is situated at Geneva, Switzerland. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for execution. Later in the year 1996 WHO (World Health Organization) has modified the guidelines proposed by ICH and WHO, in 2004 released the guidelines for stability studies in global environment. As the ICH did not assess the extreme climatic conditions found in many countries and it only covered new drug substances and the products which were earlier established. In 1997, June the United States Food and Drug Administered (US FDA) situated at Silver Spring also issued the guidelines but they were not entitled. The CDSCO (Central Drug Standards Control Organization) is a drug regulating authority for India situated at New Delhi. The regulatory requirements vary from country to country. Thus, organizing the data and scrutinizing the application became difficult. Hence, there was an urgent need to rationalize and harmonize the regulations. The ICH Steering committee was established at the meeting and A decision was to be taken at east twice a year. Series of guidelines related to stability testing have also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European agency for the Evaluation of Medicinal Products (EMEA) to assist the seeking marketing products. The Codes and Titles used in ICH[1,3] and CPMP.[1,3,12] Guidelines were tabulated in below Table

ICH codes	Guideline titles
Q1A	Stability testing of new drug substances and products (second revision))
Q1B	Photo stability testing of new drug substances and products
Q1C	Stability testing of new dosage form

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

Q1D	Bracketing and Matrixing Designs for the stability testing of drug substances and products
Q1E	Evaluation of stability data
Q1F	Stability data package for registration applications in climatic zones III and IV
Q5C	Stability testing for biotechnological/ biological products
Q6A	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

CLIMATIC ZONES FOR STABILITY STUDIES

The stability studies are performed worldwide these stability studies cannot be performed at one place as the temperature and other factors vary from country to country and place to place. Due, to this purpose the world has been divided into five zones depending on their climatic conditions so that the degradation of the product and the shelf life could be predicted accurately. Based on this data the real-time stability testing and accelerated stability testing have been derived. The standard climatic zones for the use of pharmaceutical products stability studies has enumerated and break-up of the environmental conditions derived from long term storage condition has given by WHO and ICH are also been presented in below Tables

ICH Stability Zones	
Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IVa	Hot humid/tropical zone
Zone IVb	Hot/higher humidity

2-Microbiology Analysis For Drug Stability Testing For Sterile Paracetamol Solution For Infusion 1000mg /100 Ml

OBSERVATION TABLE

Fluid Thioglycolate Medium				**Soybean Casein Digest Medium**		
Days	**Test Sample**	**Negative Control**	**Positive Control**	**Test Sample**	**Negative Control**	**Positive Control**
01	-ve	-ve	+ve	-ve	-ve	+ve
02	-ve	-ve	+ve	-ve	-ve	+ve
03	-ve	-ve	+ve	-ve	-ve	+ve

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

04	-ve	-ve	ve	-ve	-ve	+ve
05	-ve	-ve	Ve	-ve	-ve	+ve
06	-ve	-ve	ve	-ve	-ve	ve
07	-ve	-ve	ve	-ve	-ve	ve
08	-ve	-ve	ve	-ve	-ve	ve
09	-ve	-ve	ve	-ve	-ve	ve
10	-ve	-ve	ve	-ve	-ve	ve
11	-ve	-ve	ve	-ve	-ve	ve
12	-ve	-ve	ve	-ve	-ve	ve
13	-ve	-ve	ve	-ve	-ve	ve
14	-ve	-ve	ve	-ve	-ve	ve

Product Name:	**Paracetamol Solution for Infusion 1000mg /100 ml** 0 month study		
Batch Number:	**Trail 3**	**Pack size:**	100 ml
Number of Samples:	**4**		
Test Method:	Membrane Filtration		

Media used	**FluidThioglycollate Medium (FTGM) 32.5±2.50°C**	**Soybean Casein Digest Medium (TSB/SCDM) 22.5± 2.50°C**
Incubator Temperature	**32.5±2.50°C**	**22.5± 2.50°C**
Positive Control – I	S. aureus ATCC ☐	A. brasiliensis ATCC ☐
Positive Control – II	P. aeruginosa ATCC ☐	
Positive Control – III	Cl.Sporogenes ATCC ☐	C. albican ATCC ☐
Positive Control – IV	B. subtilis ATCC ☐	

OBSERVATION TABLE:

Fluid Thioglycolate Medium				**Soybean Casein Digest Medium**		
Days	**Test Sample**	**Negative Control**	**Positive Control**	**Test Sample**	**Negative Control**	**Positive Control**
01	-ve	-ve	+ve	-ve	-ve	+ve
02	-ve	-ve	+ve	-ve	-ve	+ve
03	-ve	-ve	+ve	-ve	-ve	+ve
04	-ve	-ve	ve	-ve	-ve	+ve
05	-ve	-ve	Ve	-ve	-ve	+ve

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

06	-ve	-ve	ve	-ve	-ve	ve
07	-ve	-ve	ve	-ve	-ve	ve
08	-ve	-ve	ve	-ve	-ve	ve
09	-ve	-ve	ve	-ve	-ve	ve
10	-ve	-ve	ve	-ve	-ve	ve
11	-ve	-ve	ve	-ve	-ve	ve
12	-ve	-ve	ve	-ve	-ve	ve
13	-ve	-ve	ve	-ve	-ve	ve
14	-ve	-ve	ve	-ve	-ve	ve

Product Name:	**Paracetamol Solution for Infusion 1000mg /100 ml** 3 month study		
Batch Number:	**Trail 3**	**Pack size:**	100 ml
Number of Samples:	**4**		
Test Method:	Membrane Filtration		

Media used	**FluidThioglycollate Medium (FTGM)**	**Soybean Casein Digest Medium (TSB/SCDM)**
Incubator Temperature	**32.5±2.50**ºC	**22.5± 2.50**ºC
Positive Control – I	S. aureus ATCC ☐	A. brasiliensis ATCC ☐
Positive Control – II	P. aeruginosa ATCC ☐	
Positive Control – III	Cl.Sporogenes ATCC ☐	C. albican ATCC ☐
Positive Control – IV	B. subtilis ATCC ☐	

3-Microbiological Method Validation For In Process And Finished Product Sample For Paracetamol Solution For Infusion 1000mg /100 Ml

S.no	**Challenge organisms**	**Medium**	**Incubation Temperature**	**Incubation time**
1	Staphylococcus Aureus ATCC 6538	FTGM	30 - 35°C	3 days
2	Clostridium Sporogenes ATCC 19404	FTGM	30 - 35°C	3 days
3	Pseudomonas aeruginosa ATCC 9027	FTGM	30 - 35°C	3 days
4	Bacillus Subtilis ATCC 6633	FTGM	30 - 35°C	3 days
5	Candida albicans ATCC 10231	SCDM	20 - 25°C	5 days
6	Aspergillus Brasiliensis ATCC 16404	SCDM	20 - 25°C	5 days

Post Bacteriostasis and Fungistasis Test:

This post stasis test also referred to as an inhibition test shall be performed for the following mentioned reasons:

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

To ensure that there are no inhibitory substances remining in the membrane and that the media is still capable
Of supporting the growth of the microorganisms at the end of the sterility test incubation period.
This test shell conforms the inactivation of the antimicrobial substances in the products filtered during the sterility testing.
The test shall confirm that the media inoculated with the test preparation shall support growth for the full incubation period. For example, it is necessary to show that anaerobiosis is maintained in the fluid Thioglycolate medium to allow the late development of slow growing anaerobes.
The Sterility tested canister 14 days incubation period shall be subjected to the challenge organisms. Clostridium sporogenes ATCC 19404 for fluid Thioglycolate Medium canister and Candida albicans ATCC 10231 for Soybean Casein Digest Medium shall be chosen as the challenge organism.
Quantified suspension 10-100 CFU shall be injected to the canister tubing by pre-sterilized hypodermic syringe
Fluid Thioglycolate medium canister shall be incubated at 32.5± 2.5°C and soybean Casein Digest Canister shall be incubated at 22.5± 2.5°C for a period of 5 days
If growth not apparent within 5 days for both bacteria and fungi, the test is considered invalid.

Bacterial Endotoxin Method Validation for paracetamol solution for infusion 10mg/ml

Primary Requirement:

- A calibrated Heating block capable of maintaining temperature at 37 °c ±1 °c.
- O to 200- µ 1- Micropipette.
- 100 to 1000 µ L Micropipette.
- De-pyrogenated Micro tips, 100 µ L.
- De-pyrogenated Micro tips, 1000 µ L.
- De-pyrogenated Assay tubes 10 x 75mm.
- De-pyrogenated Dilution tubes 12 x 75mm.
- Vortex Mixer.
- pH paper strips.
- 1N HCI.
- 1N NaOH.
- Test samples of three batches of the finished product which is to be validated.
- Limulus Amoebocyte Lysate
- LAL Reagent Water (LRW)
- Control Standard Endotoxin (CSE).

Identification of Critical Control Monitoring Parameter:

- Check and ensure that all the instruments are calibrated.
- Check that the personnel who is going to perform test is qualified.

Heating block temperature shall be set at 37 ^{0}C.
All the glassware & assay tubes shall be de-pyrogenated in a hot air oven.

Note: Bacterial endotoxin test procedure should be followed as mention in chapter 1

Endotoxin Limit Calculation:

Endotoxin limit = K/M

Where: K = 5 USP-EU/kg of body weight for any parenteral route of administration other than intrathecal, which is the threshold pyrogenic dose of endotoxin per kg of body weight. (Intrathecally administered products are those administered into the spinal canal so that it reaches the CSF.)

K = 0.2 EU/kg of body weight for intrathecally administered products

M = The maximum recommended bolus dose of drug per kg of body weight

Note: when the product is to be injected at frequent intervals or infused continuously, M becomes the maximum total dose administered in a single hour period.

Endotoxin limit =

Calculation of the endotoxin limit for a paracetamol solution for infusion 10mg/ml to be administered via intravenous injection at a maximum bolus dose of 4000 mg/person.
Maximum dose per kg (assuming a standard adult human body mass of 70 kg)
=4000mg/70 kg = **57.14mg/kg**
Endotoxin limit = K/M = 5 EU/kg / 57.14mg /kg = 0.0875 X 24 hours= **2.1EU/mg** endotoxin limit for paracetamol solution infusion 10mg/ml

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

4-Results

Fig: Endotoxin Reagents Used for study

Fig: positive water control shows gel clot

International Journal of Food Safety and Public Health
Vol. 12 (1), pp. 001-011, Jan-June, 2025
ISSN: 2756-3693

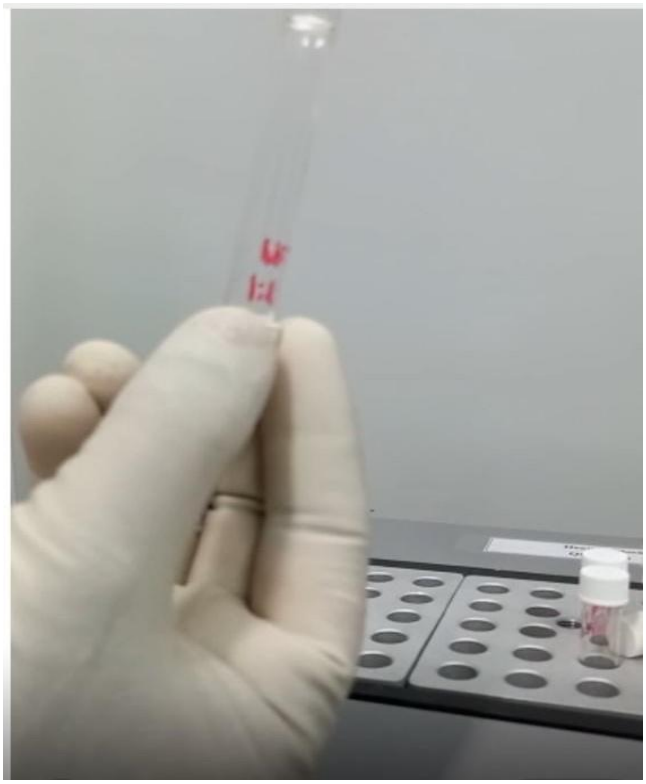

Fig: Positive product Control shows gel clot

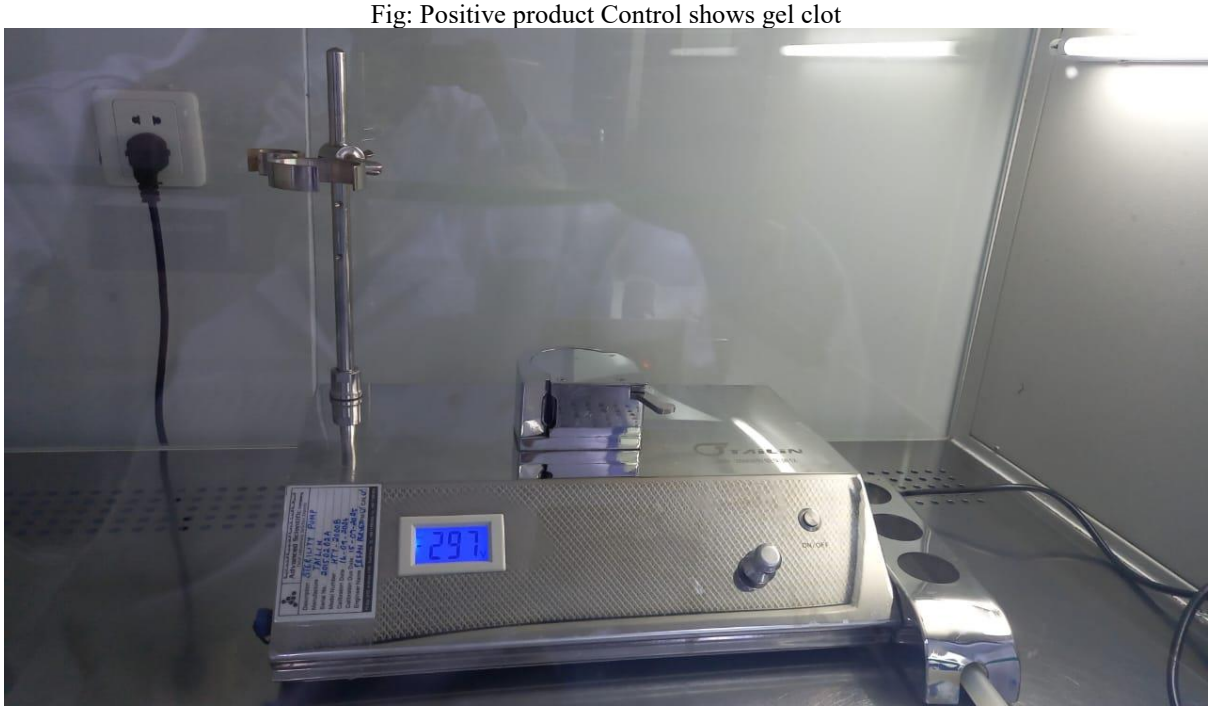

Fig: sterility pump

5- Conclusion

- The trial 1,trail 2,trail 3 batch no
- of positive control and product positive control is able to bring 75 % of recovery.
- 100 ml of non-sterile paracetamol sample size is suitable for analysis to found the contamination in the product
- Soya bean casein digest agar media is suitable for testing of non-sterile paracetamol sample.
- 0.9 % of sterile sodium chloride is suitable for rinsing of product.
- 0.45 micro membrane filter is suitable for testing

REFERENCES:

1. Markens U. (2009) Conducting Stability Studies: Recent Changes to Climate Zone IV, Life Science 13.
2. Madichie C. (2015) Designing a Smart Stability Protocol for the Global Market to Minimise Time and Cost. Informa Life Sciences' Annual Stability Testing for Pharmaceuticals and Biologics: London, UK.
3. ICH Q5C (1996) Stability Testing of Biotechnological Products. Federal Register, 36466.
4. Committee for Proprietary Medicinal Products (2001) Note for Guidance on In-Use Stability Testing of Human Medicinal Products. The European Medinces Agency: London, UK.
5. ICH Q1A (R2) (2003) Stability Testing of New Drug Substances and Products. Federal Register, 65717–65718.
6. ICH Q1B (1997) Stability Testing: Photostability Testing of New Drug Substances and Products. Federal Register, 27115–27122.
7. ICH Q1C (1997) Stability Testing for New Dosage Forms. Federal Register, 25634–25635.
8. ICH Q1D (2003) Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products. Federal Register, 2339-2340
9. ICH Q1E (2004) Evaluation of Stability Data. Federal Register, 32010–32011.
10. "Conducting stability studies - recent changes to climatic zone IV", https://www.sgs.com/~/media/global/documents/technical%20documents/sgs%20stability%20studies-en-09.pdf
11. Choudhary ankur (2010) Climatic zones for stability studies, pharmaceutical guidelines, https://www.pharmaguideline.com/2010/12/different-climatic-zones-for-stability.html
12. CFR 211.166. (2014) Stability Testing. Code of Federal Regulations. Food and Drug Administration: Rockville, MD.
13. Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. USP38–NF33. US Pharmacopeial Convention: Rockville, MD, 2014.
14. Cell and Gene Therapy Products. USP24–NF19. US Pharmacopeial Convention: Rockville, MD, 2014.
15. CPMP/QWP/609/96: (2007) Declaration of Storage Conditions. European Medicines Agency: London, UK.
16. CPMP/QWP/2934/99: (2001) In-Use Stability Testing. . European Medicines Agency: London,
17. CPMP/QWP/159/96: (1998) Maximum Shelf Life for Sterile Products After First Opening or Following Reconstitution. Committe for Human Medicinal Products. European Medicines Agency: London, UK.
18. Nita AS. (2015) Outlining Key Differences in Regulatory Requirements and Expectations for Stability Studies in Key Emerging Markets. Informa Life Sciences' Annual Stability Testing for Pharmaceuticals and Biologics: London, UK.
19. Personal correspondence with Alison Armstrong, (2015) PhD, senior director of development services at BioReliance.
20. G. Jimenez (2011) Brake B. ICH Q5C Stability Testing of Biotechnological/Biological Products. EMA Training for ASEAN, 30–31 May 2011; www.ich.org/fileadmin/Public_Web_Site/Training/ASEAN_Q5C_workshop_May_2011/SESSION_Ia_ICH_Q5C.pdf.
21. Wonnacott K. Cell Therapy Products. FDA Office of Cellular, Tissue, and Gene Therapy, Web Seminar Series; www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm241308.htm.
22. Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products. US Food and Drug Administration: Rockville, MD.
23. Kling J. (2014) Highly Concentrated Protein Formulations: Finding Solutions for the Next Generation of Parenteral Biologics. BioProcess Int. 12(5).
24. Waddle K, Pan W. Stability Studies in Pharmaceutical Development; www.catalent.com.
25. Panchal JP (2015) Analyzing Subvisible Particles in Protein Drug Products: A Comparison of Dynamic Light Scattering (DLS) and Resonant Mass Measurement (RMM). Biopharmaceutical Development and Production Week, Huntington Beach, California.
26. Neergaard MS (2014) Stability of Monoclonal Antibodies at High-Concentration: Head-to-Head Comparison of the IgG1 and IgG4 Subclass. J. Pharm. Sci. 103(1): 115–127.
27. Bott RF., Oliveira WP. (2007) Storage conditions for stability testing of pharmaceuticals in hot and humid regions. Drug Dev. and Indus. Pharm. 33:393-401.
28. Carstensen JT., Rhodes CT. (1993) Clin. Res. Drug Reg. Affairs. 10:177-185
29. Carstensen JT. (2000) Drug Stability, Principles and Practices, Marcel Dekker, New York
30. CPMP. (2003) Guideline on stability testing: Stability testing of existing active substances and related finished products. CPMP/QWP/122/02.
31. ICH Q1A (R2). (2003) Stability testing guidelines: Stability testing of new drug substances and products. ICH Steering Committee.
32. ICH Q1B. (1996) Guidance for Industry: Photostability testing of new drug substances and products. CDER, US FDA.
33. WHO. (2004) Stability studies in a global environment. Geneva meeting working document QAS/05.146 with comments.

34. USP 71 STERILITY TEST
35. USP 1211 sterilization and sterility assurance
36. USP 1227 Validation and microbial recovery from pharmacopeial articles
37 USP 85 Bacterial Endotoxins Test
38 USP 61 MICROBIOLOGICAL EXAMINATION OF NON STERILE PRODUCTS: MICROBIAL ENUMERATION TESTS