IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

"Review On Formulation And Process Validation Of Oral Solid Dosage Form Of Prothionamide Tablet"

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Abstract :

Three consecutive validation batches of Prothionamide Tablet were manufactured asperapproved batch manufacturing record. The raw materials required for these validationbatcheswere procured from approved sources and were taken up for manufacturing aftertesting andreleasebyqualitycontrol.Therawmaterialsweredispensedasperstandardoperatingprocedure. The process validation was carried out for the three batches. The critical stepsofmanufacturing such as dry mixing, wet granulation, drying, lubrication, compressionandcoating.

Keywords: Oral Dosage form, Process Validation, Preformulation, Tuberculosis.

1. INTRODUCTION.

1.1 Tuberculosis :

Tuberculosis Tuberculosis(TB) is an contagious complaint generally caused by the bacterium Mycobacterium tuberculosis. Tuberculosis generally affects the lungs, but can also affect other corridor of the body. utmost infections don't have symptoms, in which case it's known as idle tuberculosis. About 10 of idle infections progress to active complaint which if left undressed, kills about half of those infected. The classic symptoms of active TB are a habitual cough with blood- containing foam, fever, night sweats and weight loss. It was historically called consumption due to the weight loss. Infection of other organs can

beget a wide range of symptoms.(1) Mycobacterium tuberculosis(TB) is as old as the mortal species. fractions from the spinal column of Egyptian corpses dating from 2400 BC show definite pathological signs of tubercular decay. The name tuberculosis has been used from themiddle of the last century.(2)

1.2 Epidemiologyoftuberculosis

TB caused great public concern in the 19th and early 20th centuries as the aboriginal complaint of the poor. After the development of the antibiotic streptomycin in 1943, medical treatment rather than forestallment came a possibility. Prior to this medical treatment, only surgical intervention was possible along with the purported benefits of sanitaria .(3) Increases in TB numbers, seen in both the United States and Europe, were intimidating in the late 1980s, pressing the need to direct sweats on TB control. The reasons for the increases in the USA were largely attributed to the rising rates of mortal immunodeficiency contagion(HIV), worsening poverty in civic areas, drop in backing for TB control programs, and poor TB control practices. Expedients that TB could be fully excluded have been dashed since the rise ofmulti-drug resistant strains in the 1980s. In Europe, the increases were substantially associated with civic poverty. In recognition of the fact that, in both the United States and Europe, increases in TB frequence were associated with immigration from countries with high rates of TB, the complaint had to be addressed as a global issue.(4) The World Health Organization(WHO) TB remains a major public health problem worldwide declared TB and is the alternate leading cause of death due to an contagious complaint, second only to HIV/ AIDS. While important progress has been made over the once 20 times since TB was declared a public health exigency, there's still important backing demanded and work to do to control the complaint. Since 1995, further than 56 million cases have been treated for TB performing in an estimated 22 million lives saved. In addition, the global TB mortality rate has dropped by 45 compared with 1990 rates. While progress has been made, TB will continue to remain a major killer for numerous times to come(4).

The following numbers from the WHOs Global tuberculosis report 2015(5) punctuate the current state of the global TB epidemic

- Two billion people, i.e. one- third of the total mortal population, are estimated to be infected withM. tuberculosis
- 9.6 million new cases of TB passed encyclopedically in 2014 including among1.2 million living with HIV.

1.3 Pathology

TB is a bacterial infection caused by Mycobacterium tuberculosis(M. tuberculosis) also appertained to as excrescence bacilli. TheM. tuberculosis is a Gram-positive aerobic bacterium. It's a small rod- suchlike bacillus with a complex cell wall, which can repel weak detergents and survive in a dry state for weeks, but can only grow in a host organism.(6) It most generally affects the lungs, producing pulmonary TB. still, transported by the blood or lymphatic system, the TB bacilli can infect nearly any part of the body, including lymph glands, joints, feathers, and bone- redundant pulmonary TB. It's critical to understand the complaint, its etiology and its epidemiology to develop a strong TB control programmer.(7) Early

symptoms of pulmonary TB are frequently vague and fluently attributable to other conditions, with the result that numerous cases of active, contagious TB can remain undetected for some time. therefore, the complaint spreads from one person to another.(8) TB is spread when an contagious person coughs, sneezes, talks or sings, releasing driblets containing the bacilli into the air. still, TB can also be spread when TB bacilli are aerosolized by treatments, similar as flushing a crack that's infected with TB, organ transplants, or bronchoscopy. In either case, a susceptible person inhales the airborne driblets, which also cut the upper respiratory tract and bronchi to reach the alveoli of the lungs. formerly in the alveoli, alveolar macrophages take up the TB bacilli, holding some in the lungs, and transporting others throughout the body. generally within 2- 10 weeks, the vulnerable response limits further addition and spread of the bacilli.

1.4 PulmonaryTB

Pulmonary TB Pulmonary TB(PTB) is the most common and potentially most contagious type of active TB. Small areas in the lung infected with the bacilli gradationally combine to form a bigger lesion filled with infected material. This material can come liquid, which is also coughed out, leaving a depression in the lung. The process continues causing expansive damage to the lung towel and its blood vessels, generating further contagious material and inflammation – the damage to blood vessels can affect in some cases coughing up blood(hemoptysis). Some mending may do in corridor of the lung performing in scar towel. redundant pulmonary TB redundant pulmonary TB(EPTB) TB that occurs outside of the lungs and it's estimated to regard for 20 to 25% of all TB cases encyclopedically. EPTB can affect an

1.5 SignsandsymptomsofpulmonaryandextrapulmonaryTB :

The symptoms of pulmonary and extra pulmonary TB may differ but some arecommon toboth.Mostpeoplehaveonlyafewofthesesymptoms.Itisrecommendedthatanyonereporti nga cough which has lasted for two or more weeks should have their sputum tested forTB.However, for patients living with HIV, it is recommended to test their sputum forTB if theyhave had a cough of any duration. As a general rule, the presence of three ormore symptomsfortwo ormore weeks increases the suspicion of anyform ofthedisease. (12,13)

1.1 PROCESSVALIDATION:

Validation is the act of demonstrating and establishing that a procedure operates effectively. Process confirmation is the means of icing and furnishing talkie substantiation that processes are able of constantly and reliably producing a finished product of the required quality. In terms of pharmaceutical process confirmation it's intended to cover all the rudiments in a manufacturing process for a pharmaceutical product, from development of the process to final confirmation at the product scale.(14)

Some major way in the development of a Process confirmation program are as follows carrying

1) Test data to determine the numerical range of each parametere.g. assess the tablet hardness over a series of batches that achieves an respectable frangibility, decomposition, and dissolution.

2) Establishing specification limits from the test data deduced for a given parameter.
3) Determining how well the specification limit indicates that the process is under control.
4) Certifying the outfit that's used in carrying the data and controlling the process.

By careful designing and confirmation of both the process and process controls, a manufacturer can establish a high degree of confidence that all manufactured units from consecutive lots will be respectable.(14)

" **Process confirmation** is defined as the collection & evaluation of data, from the process design stage through marketable product, which establishes scientific substantiation that process is able of constantly delivering quality product ".(15) Following are the colorful generalities of process confirmation that are regulated by FDA and current GMP guidelines.(16)

- **Purpose:**This guideline outlines general principles that FDA considers to be respectable rudiments of process confirmation for the medication of mortal and beast medicine products and medical bias.
- **Scope :**This guidelines is issued under section10.90(21 CFR10.90) and is applicable to the manufacture of medicinals and medicaldevices.it countries principle and practice of general connection that aren't legal conditions but respectable to the FDA.
- **Regulatory demand** : Process confirmation is a demand of the current GMP regulations for finished medicinals 21 CRF corridor 210 and 211 and of the GMP regulations for medical bias 21 CRF corridor 820 and thus, is applicable to the manufacture of medicinals and medical bias.
- **Concept:**Generalities Assurance of product quality is deduced from careful attention to a number of factors including selection of quality corridor and accoutrements , acceptable product and process design, control of the process and in- process and end- product testing. Routine end-product testing alone frequently isn't sufficient to assure product quality for several reasons. The introductory principles of quality assurance have as their thing the product of papers that fit for their intended use.

This principle may be stated as follows

a) Quality, safety and effectiveness must be designed and erected into the product
b) Quality can not be audited or tested into finished products

Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications. Process confirmation is a crucial element in assuring that these quality assurance pretensions are met. Successfully confirmation a process may reduce the dependence upon ferocious in process and product testing.

- **The FDA defines process Validation:** Process confirmation is " establishing proved substantiation which provides high degree of assurance that a specific process will constantly produce a product meeting itspre-determined specifications and quality characteristics ". It's

important that the manufacturer prepare a written confirmation protocol, which specifies the procedures(and test) to be conducted, and the data must reflect data and be collected precisely and directly.

- **The WHO defines process Validation** : " Confirmation is proved act of proving that any procedure, process, outfit, material, exertion or system actually leads to the anticipated results. " confirmation act of proving, in agreement of GMPs that any process actually leads to anticipated results. proved substantiation that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its,
- **Defines process Validation :** confirmation is defined as " action furnishing in agreement with the principles of GMP, that any procedure, process, outfit, material, exertion or system actually lead destined specifications and quality attributes. • European commission to the anticipated results. "

RESPONABILITIES OF PROCESS CONFIRMATION(17):

Formulation development

- Laboratory function Process development
- Airman design
- Design and optimize manufacturing process
- Establish process capability information Pharmaceutical manufacturing
- Operate and maintain factory Engineering
- Installation, quality and certify factory installations, outfit and support system. Quality assurance
- Establish approviable confirmation protocols and conduct process confirmation by monitoring, slice, testing, grueling and auditing the specific manufacturing process. Regulatory affairs
- Specialized opereation representative.

1 QUALIFICATIONANDVALIDATION:

The principle of qualification and confirmation, which is applicable to the manufacture medicalproducts.it, is a demand of GMP that manufacturers identify what confirmation work is demanded to prove control of the aspects of their particular operations. Significant changes to the installations, the outfit and the processes, which may affect the quality of the product, should be validated. A threat assessment approach should be used to determine the compass and extent of confirmation.(,19)

Qualification: Action of proving that that any outfit works rightly and actually leads to the anticipated results. The word confirmation is occasionally widened to incorporates the conception qualification. the FDA guideline confirmation is a term applicable to a process, in minds of those who prepared the EC GMP companion, confirmation is applicable to " any procedure, outfit, material and system " as well as to a process.(20) The qualifications have following types

Design qualification(DQ): The thing is to perform commodity analogous to a threat analysis and to

check the design documents of a specialized system to insure that they fulfil the stoner conditions.(20)

a) **Risk analysis**- threat analysis helps to decide whether an aspect is GMP-critical or

not. Following are popular and import types of threat analysis.

b) **Failure mode effective analysis(FMEA)- FMEA:** is a quantitative threat analysis for complex systems. As this approach involves assessment of circumstance chances, discovery

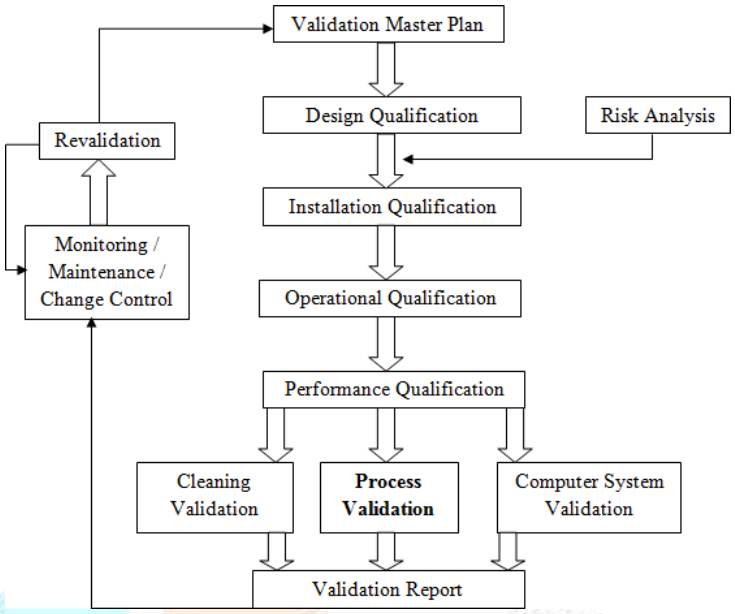

Figure1: ProcessLifeCycle (21)

1.3.1.2. Installation Qualification(Command):

During Installation qualification the performance and attestation of the specific tests are done to insure that the outfit(similar as machines, measuring outfit) used in a manufacturing process, are meetly named, rightly installed and work in agreement with established specifications.(22)

The most important aspects to consider during Command are

- Provideas-builtdocumentation.
- Checktrainingreports.
- Checkthatdocumentationiscomplete.
- Checkthatdocumentationiscomplete.
- Checkcalibrationreports

OperationalQualification(OQ)

Operationalqualificationisdefinedas“Documentedverificationthatthesystemor sub-systemperformsasintendedthroughoutallanticipatedoperatingranges.”(22)Typ icaltestsintheOQincludethefollowing:

- Alarmtests
- Behavior ofthesystemaftertheenergybreakdown
- Accuracyoffillinglines
- Transportationspeedina sterilizationtunnel
- Temperaturedistributioninanautoclave

- Performanceof awashingmachine.

Performance qualification(PQ): The PQ is the phase in which either a specialized system is tested over a long period of time(e.g., water system), or a complex specialized system is tested overall(connected stuffing line). Performance qualification should be executed by clientlabor force. The following specialized systems need to be performance- tested and qualified. High chastity water systems(monitoring of the quality parameters pH, TOC, conductivity, temperature) HVAC systems(temperature, pressure, moisture) Complex connected systems(e.g., filling line, BPI product line, performance parameters).(22) An overview of all exertion of confirmation can be understood from figure

Figure2: Overallactivity ofvalidation

1.3.2 TYPES OF PROCESS VALIDATION:

The requirements and principles are applicable to the manufacture of pharmaceutical lozenge forms. They cover the original confirmation of new process, posterior confirmation of modified process and revalidation. Process confirmation should typically be completed previous to the distribution and trade of the medical products. installations, system and outfitto be used should have been good and logical testing system should be validated(23). The colorful types of process confirmation outlined below.

1) Prospective Validation: Establishing proved substantiation previous to process perpetration that a system does what it proposed to do grounded on preplanned protocols. This approach to confirmation is typically accepted whenever the process for a new formula(or within a new installation) must be validated before routine pharmaceutical product commences. In fact, confirmation of a process by this approach frequently leads to transfer of the manufacturing process from the development function toproduction.However, similar as uniformity and identity, If change in the manufacturing process which may affect the product ‟ s characteristics.(23).

Key elementsforprospectivevalidation

i. Short description of the process.
ii. Summary of the critical processing way to be delved.
iii. List of the outfit/ installations to be used
iv. Finished product specification for release
v. List of logical styles
vi. Proposed in- process controls with acceptance criteria
vii. Testing plan viii. Functions and liabilities
viii. Proposed schedule.

2) Concurrent confirmation: Concurrent confirmation is used for establishing proved substantiation that a installation and processes do what they purport to do, grounded on information generated during factual insinuation of the process. This approach involves monitoring of critical processing way and end product testing of current product, to show that the manufacturing process is in a state of control. This is the confirmation, which carried out during product. The decision to carry out concurrent confirmation must be justified, proved approved by authorized labor force. Attestation conditions for concurrent confirmation are the same as specified for specified for prospective confirmation.(23) Following are the many aspects of Concurrent confirmation

- This confirmation comprise of determination and evaluation of process parameter applicable from scale up batch size of the product. This should be performed on 3 process confirmation batches.
- This batch should be covered for stability and quality trends.
- Previous to completion of concurrent confirmation, batches can be released for marketable distribution grounded on through monitoring and testing batches.

3) Retrospective confirmation: Retrospective confirmation is used for installations, processes, and process controls in operation use that haven't experienced a formally proved confirmation process. confirmation of these installations, processes, and process controls is possible using literal data to give the necessary talkie substantiation that the process is doing what it's believed to do. thus, this type of confirmation is only respectable for well- established processes and will be unhappy where there have been recent changes in the composition of product, operating processes, or outfit.(23) This approach is infrequently been used moment because it's veritably doubtful that any being product hasn't been subordinated to the Prospective confirmation process. It's used only for the inspection of a validated process.

Following are the many aspects of Retrospective confirmation

- The source of data for this confirmation should include. But not be limited to batch processing and packaging records, process control maps, conservation log books, records of labor force changes, process capability studies, and finished product data.
- Batches named for Retrospective confirmation should be representative of all batches made during the review period, including any batches that failed to meet specifications and should sufficient in number to demonstrate process thickness.
- For retrospective confirmation, generally data from ten to thirty successive batches should be examined to assess process thickness.

4) Revalidation Revalidation:

Means repeating the original confirmation trouble or any part of it, and includes investigative review of being performance data. This approach is essential to maintain the validated status of the factory, outfit, manufacturing processes and computer systems.(23)

Revalidation may be needed in following cases

- Change in expression, procedure or quality of pharmaceutical constituents
- Change in outfit, addition of new outfit and major breakdown
- Major change of process parameters
- Change in point
- Significant increase or drop in batch size.
- The transfer of a product from one factory to another
- Changes to the product or other changes that could affect product quality
- Significantly increase or drop in batch size.

1.3.3 STAGES OF PROCESS VALIDATION:

In November 2008, the draft publication of the FDA ‟ s long anticipated Guidance for Industry on „ Process Validation General Principles and Practices ‟. It outlines the FDA ‟ s current thinking on process confirmation for the manufacture of mortal and Veterinary medicines including Biological and APIs. The guidance states at the onset that it has been written to promote „ ultramodern manufacturing principles, process enhancement, invention, and sound wisdom ‟. From this, the guidance defines a 3- stage process for Process confirmation; Process design, Process qualification, nonstop process verification. Performing in a new description of Process confirmation(PV) as „ The collection and evaluation of data, from the process design stage throughout product, which establishes scientific substantiation that a process is able of constantly delivering quality products ‟.(24)

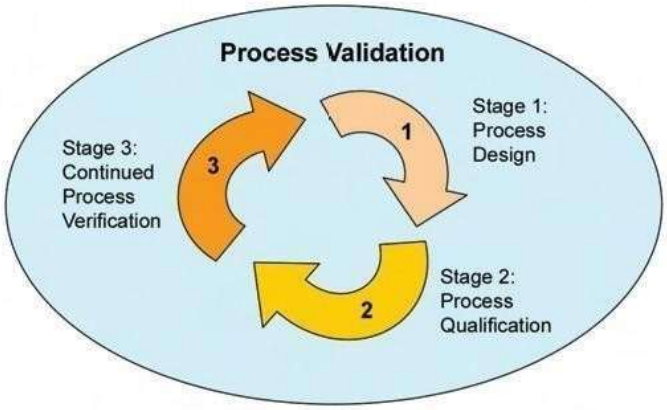

Figure 3 Process confirmation Stages

1.3.1.1 Process design

The stated thing of this stage is to „ design a process suitable for routine marketable manufacturing that can constantly deliver a product that meets its critical quality attributes(CQAs)'. The guidance again makes reference to ICH Q10, Pharmaceutical Quality Systems and draws some distinctions around the varying situations of controls needed related to the product development lifecycle conditioning.(25).

Within this integrated approach it directly recommends that the platoon responsible for Process design take early consideration of the functionality and limitations of marketable manufacturing outfit utilising their knowledge about dimension Systems in a product setting; benefactions to reuse variability from different rawMaterials or element lots; and the proposed part of the product drivers in furnishing feedback and continued process verification.(25)

1.3.1.2 Process qualification :

The stated thing is that the process design is verified as being able of reproducible marketable manufacture ‟.(26)

The USFDA ‟ s guidance further divides this stage into two rudiments

A. Design of a installation and qualification of serviceability and outfit Conditioning accepted to demonstrate that serviceability and pieces of outfit are suitable for their intended use and perform duly are appertained to in this guidance as qualification
.(26).
B. Performance qualification- „ Confirm the process design and demonstrate that the marketable manufacturing process performs as anticipated ‟.(26)

1.3.3.3 Continuousprocessverification:

The aim of the third process confirmation stage is to „ continually assure that the process remains in a state of control(the validated state) during marketable manufacture ‟. This will bear robust systems for detecting unplanned departures from the designed process and there's a strong emphasis on statistically

trended data which is reviewed in a timely manner by trained labor force. It highlights that conservation of the installation, serviceability, and outfit is another important aspect of icing that a process remains in control.(26) Strategy for Artificial Process confirmation of Solid Lozenge Forms(26)

1.3.4 The strategy named for process confirmation should be simple and straightforward. The following five points gives strategy for process confirmation

- The use of different lots of raw accoutrements should be included. i.e. active medicine substance and major excipients.
- Batches should be run in race and on different days and shifts(the ultimate condition, if applicable).
- Batches should be manufactured in the outfit and installations designated for eventual marketable product.
- Critical process variables should be set within their operating ranges and shouldn't exceed their upper and lower control limits during process operation. Affair responses should be well within finished product specifications.
- Failure to meet the conditions of the confirmation protocol with respect to process input and affair control should be subordinated to process requalification and posterior revalidation following a thorough analysis of process data and formal discussion by the confirmation platoon.

1.3.5 WHY VALIDATE PROCESSES

In addition to the nonsupervisory conditions, for validating processes, a manufacturer can assure through careful design of the device and packaging, careful design and confirmation of processes, and process controls, that there's a high probability that all manufactured units will meet specifications and have invariant quality. A duly validated and controlled process will yield little scrap or rework, performing in increased affair. Also, when demanded, the confirmation lines contain data to support advancements in the process or the development of the coming generation of the process.(14)

PREFORMULATION STUDIES :

The preformulation study like characterization of medicine sample which includes physical characterization and logical methodologies, and evaluation of tablet mix including determination of bulk viscosity, tapped viscosity, compressibility indicator, Hausner rate and LOD were performed for expression mix.

A. **Physical Characterization of medicine** :

The Sample The sample of Prothionamide greasepaint medicine was arranged from Pen TSAO Chemical and was characterized for its identification and authenticity. The medicine was physically characterized according to following styles.

B. Description:

The sample of Prothionamide was subordinated to the following tests for its characterization Nature of the medicine sample The medicine sample was observed visually and viewed under the emulsion microscope for the determination of its nature and also the results were compared with the sanctioned books.

C. Color of the medicine sample:

The medicine sample was viewed visually for the determination of its color using the black and white backgrounds and also the results were compared with the sanctionedbooks.

D. Melting point of the medicine sample:

The Melting point is one of the important styles for identification of medicine sample. Melting point of the medicine sample was determined by capillary system by using Melting point outfit. evidence of medicine evidence of medicine was carried out by usingX-Ray diffraction, Thin Subcaste Chromatography.

1.2 Evaluation of Blend:

Evaluation of mix's for fast dissolving tablet of different expression were bandied as follows Pre-compression Parameters deduced parcels Preformulation testing is an disquisition of physical and chemical parcels of a medicine substances alone and when combined with excipients. It's the first step in the rational development of lozenge forms. The overall ideal of preformulation testing is to induce information useful to the expression in developing stable and bioavailable lozenge form.

1.2.1 Bulk Density:

Bulk Density is defined as weight per unit volume. Bulk viscosity(Pb) is defined as the mass of the greasepaint divided by the bulk volume and is expressed as gm/ cm3. The bulk viscosity of a greasepaint primarily depends on flyspeck size distribution, flyspeck shape and the tendency of patches to cleave together. There are two types of bulk viscosity. The patches are packed in such a way so as to leave large gaps between their shells performing up in light greasepaint of low bulk viscosity. Then the lower patches shift between the large patches performing in heavy greasepaint of high bulk viscosity. Bulk viscosity is veritably important in the size of holders demanded for running, shipping, and storehouse of raw material and mix. It's also important in size blending outfit. Apparent bulk viscosity(Pb) was determined by pouring mix into a graduated cylinder. The bulk volume(Vb) and weight of the greasepaint M) was determined.

The bulk viscosity was calculated by using the following formulaPb = M/ Vb

Where, Pb = Bulk viscosity, M = Weight of sample in gm,Vb = Final volume of mix in cm

1.2.2 Tapped viscosity:

Tapped viscosity is achieved by mechanically tapping a measuring cylinder containing the greasepaint sample. After observing the original volume, the cylinder is mechanically tapped and volume reading is taken until little farther volume changes are observed. The mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight a specific distance. Device that rotates the cylinder during tapping may be preferred to minimize any possible separation of the mass during tapping down. It's the rate of total mass of the greasepaint to the tapped volume of greasepaint. Tapping was done up to time there's no farther movement of volume was noted.

The tapped viscosity was calculated by using the following formula

Pt = M/ VtWhere, Pt = Tapped viscosity, M = Weight of the sample in gm, Vt = tapped volume of mix in cm.

1.2.3 Carr's indicator or Compressibility:

The simplest way for dimension of free inflow of greasepaint is compressibility, an suggestion of the ease with which a material can be convinced to inflow is given by compressibility indicator(I) which was calculated as follows

$I = Pt – Pb/ Pt \times 100$

Where,

I = Carr's indicator or CompressibilityPt = Tapped viscosity

Pb = Bulk viscosity

1.2.4 Hausner ratio:

Hausner rate is an circular indicator of ease of greasepaint inflow. It wascalculated by the following formula

Hausner ratio = Pt/ Pb

Where, Pt = Tapped viscosity, Pb = Bulk viscosity

1.2.5 Loss On Drying:

This is employed in IP, BP, USP. Although the loss in weight, in the sample so tested, basically is due to water and small quantum of other unpredictable accoutrements will contribute u weightloss., it's suitable where large no of sample are handled and where a nonstop record of loss in weight with time is needed. Weigh the importing bottle preliminarily dried at 105 °C(W1). place 1gm of sample in importing bottle and weigh the importing bottle with sample(W2), put the importing bottle with sample in an roaster maintained at 105 ± 2 °C and at a pressure 5 mm of hg. Sot the sample for 3 hours. After completion of 3 hours, open the drying roaster, take out the bottle cool in desicators. Weigh the bottle and content(W3g) The Loss On Drying is calculated by the formula,

1.2.6 For Dried grains:

Residual Detergent(Methanol) By Gas Chromatography : Blank Preparation Pipette out 1 ml of dimethylsulfoxide in to a vial. Seal with a septum and crimp cap. Standard result Weigh directly about 240 mg of Methanol in a 50 mL volumetric beaker containing about 20 mL of dimethylsulfoxide. Dissolve and adulterate to the volume with the same detergent. Pipette out5.0 ml of this result in a 50 mL volumetric beaker, adulterate to the volume with dimethysulfoxide. Pipette out 1 mL of the result in to a vial and seal with a Septum and crimp cap. Test Preparation Weigh and transfer about2.0 g of mix to a 50 ml volumetric beaker, add about 20 ml of dimethylsulfoxide and sonicate it to disperse. also adulterate to volume with dimethylsulfoxide. Centrifuge the result for 5 twinkles at 3000 rpm in breach test tube and transfer1.0 ml of the supernatant result to headspace vial. Crimp it and keep for injection.

Chromatographicsystem:

Instrument :PerkinElmerAutosystemGasChromatograph.

Column :DB-624, Dia.0.53mm, 60mtr, 3.0 □m. Fused silica capillary,Detector :FlameionizationDetector(FID)

Carriergas :Nitrogen /Helium

Gas Chromatograph parameters Carrier gas Pressure5.0 psig. Sensor temperature 250 temperature range 1 Attenuation 64 Procedure Set up the GC according to the operating parameters and disequilibrate the column until the stable birth is attained. fit blank medication followed by six replicate injections of standard medication. Record the chromatograms and calculate systemfelicityparameters.For waxed grains

1. Water Content Determine the test on0.5 g of the sample using Karl Fischer outfit. Reporting Report the results as w/w.
2. Mix uniformity by HPLC Instrumental Conditions ColumnInertsil ODS 3V(150 X4.6) mm, 5µ or original Flow Rate1.2 ml/min. Wavelength
   257 nm Injection Volume 20 µl Column Temperature 30 °C Runtime8.0min. bus sample temperature 10 °C

Preparation of buffer :Dissolve3.9 gm of Sodium dihydrogen phosphate dihydrate and 2 ml of Trimethylamine in 1000 ml of water; acclimate pH to2.5 ±0.05 with orthophosphoric acid. Mobile phase Mix buffer and acetonitrile in the rate 6040). Diluent medication Mix 5 ml of Triethylamine to 500 ml of water, add 500 ml of Acetonitrile and blend.

Standard Preparation: Weigh directly 80 mg of Prothionamide WS into a 200 ml volumetric beaker, add 70 ml of diluent, sonicate for 5 twinkles with intermittent shaking, cool to room temperature and adulterate up to the Mark with diluent. Further dilute5.0 ml of result to 25 ml with diluent and blend.(Prepare the standard medication in duplicate for determination of similarity factor- relate note)

Test Preparation for mix uniformity : Weigh directly the vial containing mix. Record the gross weight(G). Transfer the entire content of the vial into the 200 ml volumetric beaker. wash the vial thrice with 5 ml of diluent and add the washings into the volumetric beaker. Sot the bottle at 80 °C for three hours, cool and determine its tare weight(T). Determine the net weight of the contents(G- T). Add about 100 ml of diluent and sonicate for 15 twinkles in cold water with intermittent shaking. Cool to the room temperature and adulterate to volume with diluent and blend. Centrifuge this result at 5000 rpm for 5 twinkles. Further dilute10.0 mL of supernatant result to 25 mL with diluent and sludge this result through1.0 µ SGF hype

Prepare the test medication in single: Test Preparation for Composite mix Weigh and transfer mix original to 400 mg of Prothionamide to 500 ml volumetric beaker, add 100 ml of diluent and sonicate for 10 twinkles with intermittent shaking in cold water. also add 200 ml of diluent and sonicate for 5 twinkles with intermittent shakingin cold water. Cooled to room temperature and adulterated up to the make with diluent. Centrifuge this result at 5000 rpm for 5 twinkles. Further dilute5.0 ml of supernatant result to 50 ml with diluent and sludge through1.0 µ SGF hype

Note- Standard and sample result is stable up to 48 hrs. at 10 °C.

Procedure

Set up the HPLC according to the operating parameters and disequilibrate the column until the stable birth is attained. fit the results, record the chromate orgasm and measure the peak area responses for the major peaks. Evaluation of Tablet Evaluation result for Prothionamide tablet of different expression were bandied as follow Hardness Select 10 tablets from pooled sample and measured the hardness of tablet using calibrated hardness tester like Monsanto hardness tester or schleuniger hardness tester. Frangibility The frangibility of tablets was determined using Roche Friabilator. PreweighedProthionamide tablets were transferred into friabilator. The friabilator was operated at 25 rpm for 4 twinkles

i.e. 100 revolutions. Tablets are dropped from a distance of 6 elevation with each revolution. The tablets were subtracted and counted again. The chance frangibility was calculated by, Consistence Tablet consistence was measure by calibrated Vernier caliper scale and is measure in mm. Average Weight Select 20 Tablets aimlessly from the pooled sample. Weigh 20 tablets collectively and calculate the average weight. Report the value in mg. Total Weight of 20 tablets Average weight = 20 Decomposition Test Decomposition test was performed on 6 tablets. Place one tablet in each of the six tubes of the handbasket, add slice to each tube and operate the outfit using water at 37 ± 2 °C as the absorption fluid. At the end of 30 twinkles, lift the handbasket from the fluid and observed the tablets. All the tablets should disintegrate. Record the decomposition time in nanosecond andseconds.However, repeat the test on 12

fresh tablets not lower than 16 of the aggregate of 18 tablets should disintegrate, If 1 or 2 tablets are fail to disintegrate. Water Content Crush 10 tablets veritably finely and determine the test on0.2 g of sample using Karl Fischer outfit. Reporting Report the results as w/w.

Dissolution: Dissolution parameters outfit Paddle, USP Type 2 Speed 75 RPM Medium pH7.5 Phosphate buffer Time 30min. Volume withdrawn 10 ml Temperature 37 °C ±0.5 °C Medium Volume 900 ml. Diluent medication Mix 5 ml of Triethylamine to 500 ml of water, add 500 ml of Acetonitrile and blend. Dissolution medium medication Prepared by dissolving13.61 g of potassium dihydrogen phosphate in about 800 ml of water, conforming with 2M sodium hydroxide to a pH of7.5 and lacing with water to 1000 ml. Standard Preparation Weigh directly 67 mg of Prothionamide WS into a 100 ml volumetric beaker, Add 70 ml of diluent and sonicate in cold water for 5 twinkles to dissolve, adulterate to volume with diluent and blend. Further dilute5.0 ml of this result to 250 ml with dissolution medium.(Prepare the standard medication in duplicate for determination of similarity factor- relate note) Test result Place the pronounced volume of the dissolution medium in each vessel of the outfit. Warm t dissolution vessel containing separate dissolution medium. incontinently operate the outfit at specified speed. At the end of specified time interval, withdraw about 10 ml of aliquot of each instance from a zone interior between the face of the dissolution medium and top of the rotating paddle, not lower than 1 cm from the vessel wall and sludge through a sludge having a porosity of1.0 µ SGF hypediscarding first many ml of the filtrate. Further dilute 6 ml of this result to 10 ml with dissolution medium. Procedure Measure the absorbance of standard in five replicates and test medication at 296 nm by using suitable UV spectrophotometer against dissolution medium as blank.

8.3.9Uniformityof dosageunits(byContentuniformity)byHPLC

Test Preparation: Transfer 1 tablet into a 100 ml volumetric flask, add 30 ml of diluentandsonicate till the tablet get completely dispersed with intermittent shaking in cold water. Thenadd30mlofdiluentandsonicatefor5minuteswithintermittentshakingincoldwater.Cooledto room temperature and diluted up to the make with diluent. Centrifuge this solution at 5000rpmfor5minutes.Furtherdilute10.0mlofthesupernatantsolutionto25ml;withdiluentandfilte rthrough 1.0 µ SGF syringefilter.

Solution Stability: Standard and sample solutions are stable up to 48 hours at 10°C.**Procedure:** Set up the HPLC according to the operating parameters and equilibrate thecolumn until the stable baseline is obtained. Inject the solutions, record the chromatogramsand measure the peak area responses for the major peaks. The approximate retention time fortheProthionamidepeak is about 4.7 minutes.

MICROBIOLOGICALEXAMINATION:

Performtheteston10gofsample.

Reporting: i)ForMicrobialEnumerationTest:Reportsthevalue incfu/g. ii)ForSpecifiedmicro-

organismTest:ReportasPresent/Absent.

RESIDUALSOLVENT(Methanol):

BlankPreparation: Transfer1.0mlofthedimethylsulfoxideintoaheadspacevial,Sealwithaseptumand crimp cap.

Standard Preparation: Weigh accurately about 400 mg of Methanol in a 100mL volumetricflaskcontainingabout30mLofdimethylsulfoxideanddilutetothevolumewithdimethyl sulfoxide. Pipette out 5.0 ml of this solution in 50 ml volumetric flask and dilute tomark with same solvent and mix well. Transfer 1.0 ml of this solution in to a headspace vial.Sealwith aseptum and crimp cap.

Test Preparation: Break and transferred weighed 10 tablets in a 50 ml volumetric flask,containingabout30mlofdimethylsulfoxideandsonicatetodispersethetabletswithintermitten tshakingforanabout10-20minutes.Diluteuptothemarkwithdimethylsulfoxide.Centrifuge at 3000 rpm for 5 minutes. Transfer 1.0 ml of the supernatant solution in to aheadspacevial, sealwith aseptum and crimp cap.

Chromatographicsystem:

Instrument: Perkin Elmer Clarus 500 system Gas Chromatograph.Column:DB-624, Dia.0.53 mm, length:60mtr,3.0 Γm.
Detector:FlameionizationDetector(FID)

Carrier gas: Nitrogen / Helium Gas Chromatographparameters:Carriergas Pressure: 5.0psig.
DetectorTemperature:250C

Injector Temperature : 200CDetector RangeLimitofQuantification(LOQ): 60µg/tablets

Procedure: Set up the GC according to the operating parameters and equilibrate the columnuntilthestablebaselineisobtained.Injectblankpreparationfollowedbysixreplicat einjectionsof standard preparation, then blank preparation in single. Record thechromatograms andcalculatesystem suitabilityparameters.Limits areasfollows, Tailingfactor ofMethanol peak shouldnot be morethan 2.0

Relative standard deviation for area of six replicate injections of standard preparationshouldnotbe morethan 15.0%.

If system suitability passes then make duplicate injections of test preparation andrecord thechromatograms.

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