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# Stability Study Of Optimized Formulation

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**ABSTRACT**

Stability Design: In any rational design and evaluation of dosage forms for drug products, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. Or Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a pre-determined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The stability studies were carried as per ICH guidelines. The accelerated study was carried at temperatures of 40°C±2°C/75%±5% RH and real time condition was carried at temperatures of 25°C±2°C/60%±5% RH sample with drawn at respective intervals of 1st month, 2nd month, 3rd month at accelerated condition at real time condition for evaluation parameters such as description, assay, related substances and dissolution profile.

**Keywords**: Optimized Formulation, T-114, Taste masking, Dissolution Profile, polymethacrylate copolymer

## INTRODUCTION:

The present study focus is on the "novel practical approcahes[1-5] of taste masking of novel antibacterial bitter drug for better patient compliance – some techniques evaluation and characterization".

The drug candidate, Linezolid is an antibacterial drug being used as first line treatment while treating infection. The drug candidate is proven clinically safe and effective via oral route. However, the drug candidate has bitter taste which can't be swollen without masking the bitter taste. The taste needs to be masked in such way that the drug candidate retains its original properties and at the same time taste masked granules of Linezolid will be formulated tablet and also as dry suspension for further evaluation. The objective of this study was to mask the bitter Linezolid using four different techniques with four polymers. Ion exchange resins, Eudragit polymer, betacyclodextrin and glyceryl palmitostearate were used as taste masking agents. Resin drug complexation, Complexation using betacyclodextrin, microsphere using eudragit polymer and melt granulation using glyceryl palmitosterate were the technique followed to assess for the best possible bitter taste masking. The tablets were formulated using direct compression from the drug resin complex and microsphere based granules. The dry suspension was made using betacyclodextrin complex and melt granulated using glyceryl palmitosterate.

Further, The required granules were evaluated for flow properties. The formulated tablets[6-10] were evaluated for important parameters and also for critical parameters like, dissolution profile, taste evaluation, disintegration, etc. The dry suspension after reconstitution was subjected for critical evaluation like sedimentation volume, viscosity, pH, dissolution profile etc.

The analytical method[11-16] was developed and validated meeting the requirements. The quality by design concept was overall evaluated in the present research topic. Also the stability study per ICH guidelines was conducted on the optimized formulations of two tablet two dry suspension formulations.

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**Table No.1: Stability Design of Taste Masked Linezolid Tablets & Dry Powder Suspension:**

| S No | Test | 40°C ± 2°C/75% RH | | | 25°C ± 2°C/60% RH |
|---|---|---|---|---|---|
| | | 1M | 2M | 3M | 3M |
| 1. | Description | ✓ | ✓ | ✓ | ✓ |
| 2. | Assay By HPLC | ✓ | ✓ | ✓ | ✓ |
| 3. | Related substances | ✓ | ✓ | ✓ | ✓ |
| 4. | Dissolution Profile | ✓ | ✓ | ✓ | ✓ |

**STABILITY STUDY OF OPTIMIZED FORMULATION:** [17-19]

**Table No. 2. - TEST PARAMETERS TO BE EVALUATED**

| S. No: | TEST | SPECIFICATION (for information only) |
|---|---|---|
| **1.** | Description | **White to off white tables** |
| **2.** | Assay of by HPLC | **Between 90 and 110%** |
| **3.** | Related substances by HPLC | |
| | Known Impurities | NMT 0.2% each |
| | Single maximum unknown Impurity | NMT 0.20% |
| **4.** | Total Impurities | NMT 1.0% |
| **5.** | Dissolution Profile | NLT 80 Q in 45Minutes |

Note: The above test parameters for evaluation is applicable for tablets.

**Table No. 3: Preformulation Study Results**

| Sl. No. | Test Parameter | Results |
|---|---|---|
| **1.** | Description | Complies |
| **2.** | Identification by IR | Complies |
| **3.** | Melting point by DSC | 180.0°C |
| **4.** | Solubility | *Solubility Profile in Common Solvents:*<br>Solvent \| Solubility (mg/ml) LINEZOLID \| Descriptive term (as per USP)<br>Water \| 2.01 \| Slightly soluble<br>Methanol \| 20.85 \| Sparingly soluble<br>Dichloromethane \| 62.65 \| Soluble<br>Dilute Hydrochloric acid \| 250.10 \| Freely soluble<br>*Quantitative Aqueous Solubility Profile:*<br>Solvent \| Solubility (mg/ml) LINEZOLID API \| Descriptive term (as per USP)<br>1.1 – 0.1 N HCl \| 10.01 \| Sparingly soluble<br>4.5-USP Acetate buffer \| 2.00 \| Slightly soluble<br>6.8-USP Phosphate buffer \| 2.86 \| Slightly soluble<br>7.5-USP Phosphate buffer \| 2.00 \| Slightly soluble |
| **5.** | Loss on Drying | NMT 0.50% |
| **6.** | Hygroscopic study | Material was not Hygroscopic |
| **7.** | XRD Study | The result conformed to the standard used in the test and conforming to the polymorph |

**ANALYTICAL METHOD VALIDATION OF ASSAY, RELATED SUBSTANCES AND DISSOLUTION TEST PARAMETERS** [11-14]

Parameters considered for analytical method validation of Assay method for Linezolid Formulations.

The following parameters were considered for analytical method validation of Assay method in the drug product Linezolid formulations.

System suitability

Specificity

Forced degradation

Precision

System precision

Method precision

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Intermediate precision

Stability in analytical solution

Linearity

Accuracy

Range

Robustness

**DETAILS OF DRUG SUBSTANCE:**

Chemical Structure:

Linezolid:

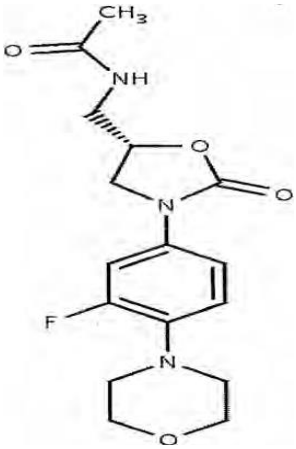

**Figure No.: 1:** Structure of Linezolid

Molecular formula and weight : $C_{16}H_{20}FN_3O_4$, and 337.3461 g/mol

CAS Number : 165800-03-3

**Chemical Name :** N-{[(5S)-3-[3-fluoro-4-(morpholin-4-yl) phenyl]-2-oxo-1, 3-oxazolidin-5-yl]methyl}acetamide

REAGENTS, STANDARDS, IMPURITIES AND SAMPLES USED:

**Table No.:4** Reagents Details

| S.No. | Reagent |
|---|---|
| 1 | Monobasic Sodium Phosphate ($NaH_2P0_4$) |
| 2 | Acetonitrile |
| 3 | Water |

**Table No.: 5** Details of Standards/Impurities:

| S.No. | Standard/Impurity |
|---|---|
| 1 | Linezolid working Standard |
| 2 | Impurity-B |
| 3 | Impurity-C |
| 4 | Impurity-D |
| 5 | Impurity-I |
| 6 | Impurity-II |

**Table No.: 6:** Details of Sample:

| S.No. | Sample |
|---|---|
| 1 | Linezolid Formulations |

**Note:** All the materials used were within the expiry date and stored at recommended storage conditions.

METHOD DESCRIPTION:

**Principle:** Reverse phase liquid chromatography with Isocratic elution and UV detector.

**Table No.: 7:** Chromatographic conditions

| | | |
|---|---|---|
| Column | : | YMC Hydrosphere C18, 4.6 x 150 mm, 5µ or equivalent |
| Wavelength | : | 254 nm |
| Injection volume | : | 10 µL |
| Column Temperature | : | 25°C |
| Sample try Temperature | : | 25°C |
| Flow rate | : | 1.0 mL/min |
| Run Time | : | 10 minutes |
| Diluent | : | Mobile phase |

**Mobile Phase Preparation:**

**Buffer:**

Weigh and transfer 4.7g of monobasic sodium phosphate into l000 mL of water. Dissolve and mix.

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**Mobile Phase:**

Mix 800 mL of buffer and 200 mL of Acetonitrile, Filter and degas by sonication.

**Preparation of Standard**

Weigh and transfer about 20 mg of Linezolid standard into 50 mL volumetric flask, dilute to volume with diluent and mix well. Further dilute 5.0 mL of this solution to 25 mL with diluent.

**Preparation of Sample**

Weigh accurately 10 tablets and transfer these tablets into 200 ml amber colour volumetric flask, add 150ml of diluent and sonicate it for 15 minutes; allow it to cool at room temperature. Make up the volume up to the mark with diluent. Dilute 4 ml of this solution to 50 ml with diluent. Filter the sample the sample solution through 0.45□ Nylon filter.

**Procedure**

Inject Diluent (one injection), then inject five replicate injections of standard preparation and check the system suitability parameters.

**System suitability:** Acceptance criteria

The % RSD for the area of Linezolid replicate injections of standard preparation should be NMT 2.0.

Theoretical plates for Linezolid peak should be NLT 1500.

Tailing for Linezolid peak should be NMT 2.0.

If system suitability parameter passes then inject sample preparation (duplicate injections). Record the area from the chromatograms and calculate the assay.

**Calculation and Formulae:**

For calculation and formulae, refer section 15.0.

Calculate the % assay of Linezolid by the following formula:

$$\%\text{Assay} = \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{V} \times \frac{P}{100} \times \frac{100}{LA}$$

Where,

AT : Average area of Linezolid peak from the Sample chromatogram.

AS : Average area of Linezolid peak from the standard chromatogram

WS : Weight of Linezolid Standard in mg.

DT : Dilution of sample in mL.

DS : Dilution of standard in mL.

V : Volume of sample taken (mL)

P : % purity of Linezolid standard

LA : Label Amount

**SYSTEM SUITABILITY:**

To verify the analytical system is working properly and can give accurate and precise results, the system suitability parameters are to be set.

Injected Diluent (one injection) and Standard preparation (5 injections), recorded chromatograms and checked the system suitability parameters.

**Table No.: 8:** System suitability details

| Acceptance criteria | Results |
|---|---|
| The % RSD for the area of Linezolid replicate injections of standard preparation should be NMT 2.0. | 0.1 |
| Theoretical plates for Linezolid peak should be NL T 1500. | 10286 |
| Tailing factor for Linezolid peak should be NMT 2.0 | 1.2 |

Data interpretation:

From the above results, it can be concluded that the system is suitable for analytical method validation.

**SPECIFICITY:**

Specificity is the ability of analytical method to assess unequivocally the analyte in the presence of component that may be expected to be present, such as impurities, degradation products and matrix components.

Performed the specificity parameter of the method by injecting Diluent, Standard preparation, Sample preparation> Placebo preparation, known impurities and Sample spiked with impurities into the Chromatographic system and recorded the Retention times.

**Acceptance Criteria:**

Diluent, placebo and impurities peaks should not interfere with Linezolid peak.

The peaks of Impurities and Linezolid should not interfere with each other.

**Table No.: 9** Retention Time Details

| Solutions | | Retention time (in min.) |
|---|---|---|
| Diluent | | - |
| Placebo preparation | | - |
| Standard preparation | | 6.193 |
| Sample preparation | | 6.143 |
| Impurity-I | | 22.213 |
| Impurity-II | | 12.933 |
| Impurity-B | | 4.510 |
| Impurity-C | | - |
| Impurity-D | | 3.227 |
| Sample | Impurity-I | 22.073 |
| | Impurity-II | 12.860 |
| | Impurity-B | 4.503 |
| | Impurity-D | 3.230 |
| | 5-HMF | 2.397 |
| | Linezolid | 6.153 |

Data interpretation:

From the above results, it can be concluded that there is no interference of diluent, placebo and impurities peaks with Linezolid peak.

**SPECIFICITY BY DEGRADATION STUDIES:**

**Specificity by forced degradation:**

Forced degradation of Linezolid injection has been carried out, to confirm that during stability study or throughout the shelf life, any degradation if found should not interfere with the Linezolid peak. In addition the forced degradation study will help to identify the type of degradation pathway (whether oxidative, alkali hydrolysis, acid hydrolysis, water hydrolysis, photolytic and dry heat) for each of the degradants.

**Preparation of Sample:**

Sample as such: Taken 2 mL sample solution into 50 mL volumetric flask, dissolved, and diluted to volume with diluent.

**Placebo as such:** Taken 2 mL Placebo solution into 50 mL volumetric flask, dissolved, and diluted to volume with diluent.

**Neutral Stressed sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask, added 2 mL water to it and kept it in water bath at 80°C for 4 hours. Allowed it to attain room temperature, then diluted to the volume with diluent.

**Acid Stressed sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask, added 2 mL 0.1 N HCI to it and kept it in water bath at 80°C for 4 hours. Allowed it to attain room temperature. Neutralized with 2 mL of 0.lN NaOH, then diluted to the volume with diluent.

**Repeated the same with IN HCl.**

**Alkali Stressed sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask, added 2 mL O.lN NaOH to it and kept it in water bath at 80°C for 4 hours. Allowed it to attain room temperature. Neutralized with 2 mL of 0.1 N HCL, then diluted to the volume with diluent.

**Repeated the same with lN NaOH.**

**Peroxide Stressed sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask, added 2 mL 3% Peroxide to it and keep it in room temperature for 7 days. After 7 days, diluted to volume with diluent and mixed well.

**Sunlight exposed sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask and exposed to Sunlight for 8 hours and diluted the volume with diluent.

**UV light exposed sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask and exposed to an illumination of 1.2 million Lux hours of cool fluorescent light and an integrated near UV energy exposure of 200-Watt hours/$m^2$, simultaneously in photo stability chamber maintained at 25°C.Then dilute to volume with diluent.

**Thermal Stressed (Dry heat) sample:**

Taken 2 mL Sample solution into 50 mL volumetric flask and exposed to hot air oven at 80°C for 8 hours, cooled to room temperature then diluted the volume with diluent.

**Note:** The same treatment should be made for placebo.

**Acceptance criteria:**

Peak of Linezolid should be pure.

All known and unknown impurity/Degradation products if any should be well separated from the Linezolid peak.

Peak purity factor for Linezolid peak should be NLT 0.990.

**Table No.: 10. Forced degradation study compilation**

| Stressed Condition | Linezolid (in Assay%) | Linezolid (% of Degradation) |
|---|---|---|
| Sample As such | 101.9 | - |
| Alkali | 76.4 | 25.0 |
| Acid | 72.1 | 29.2 |
| Peroxide | 91.9 | 9.7 |
| Neutral | 98.9 | 2.9 |
| Sun light | 102.3 | - |
| UV-light | 101.5 | 0.4 |
| Thermal | 101.6 | 0.3 |

**Data Interpretation:**

The Sample is found to be degrading in acid, alkali, peroxide and neutral stressed conditions but slightly degraded in UV, sunlight and thermal stressed condition. However, unknown impurities are well separated from Linezolid peak and impurities. The Linezolid peaks are pure. Hence, the Assay method is considered specific & stability indicating.

**PRECISION:**

The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple sampling of homogeneous sample. The precision of analytical method is usually expressed as the standard deviation or relative standard deviation (Coefficient of variation) of series of measurements.

**SYSTEM PRECISION:**

The system precision is checked by using standard chemical substance to ensure that the analytical system is working properly. The retention time and the area response of six determinations should be measured and calculated relative standard deviation.

Injected diluent one injection and standard preparation six injections into the chromatograph. Recorded and calculated relative standard deviation.

**Acceptance criteria:**

The %RSD of the Retention time for the Linezolid peak obtained from 6 injections of standard preparation should be NMT 1.0

The %RSD of the Area response for the Linezolid peak obtained from 6 injections of standard preparation should be NMT 2.0

**METHOD PRECISION:**

In method precision, a homogeneous sample of a single batch should be analyzed six times. This indicates whether a method is giving consisting results of a single batch.

Analyzed the samples of Linezolid formulations six times of a same batch as per analytical procedure. Calculated the % Assay of Linezolid.

Acceptance Criteria:

The% RSD of the calculated Assay results for 6 determinations should be NMT 2.0

**Table No.:11.** Percentage assay results of Linezolid in assay test parameter validations

| Sample | % Assay of Linezolid |
|---|---|
| 1 | 101.1 |
| 2 | 101.5 |
| 3 | 101.5 |
| 4 | 101.5 |
| 5 | 101.3 |
| 6 | 101.2 |
| Mean | 101.4 |
| % RSD | 0.2 |

**Data Interpretation:**

From the above results, it can be concluded that the method is precise.

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STABILTY IN ANALYTICAL. SOLUTION:

Evaluate the stability in analytical solution by injecting the standard preparation and sample preparation at regular interval.

Acceptance criteria:

The % difference of Area Response for the peaks in Standard preparation and Sample preparation should be within± 2.0% from initial area after specified period.

Standard and samp1e preparation stability at 25°C:

**Table No.: 12: Solution Stability Details**

| Linezolid | | | | | |
|---|---|---|---|---|---|
| Standard preparation | | | Sample preparation | | |
| Time (in hours) | Area response | % Difference | Time (in hours) | Area response | % Difference |
| Initial | 2648454 | - | Initial | 2632827 | |
| 3 | 2630435 | -0.7 | 2 | 2621526 | |
| 6 | 2631686 | -0.6 | 5 | 2623360 | |
| 8 | 2634353 | -0.5 | 7 | 2625299 | |
| 10 | 2633493 | -0.6 | 10 | 2624169 | |
| 13 | 2635801 | -0.5 | 12 | 2628053 | |
| 15 | 2634647 | -0.5 | 14 | 2629503 | |
| 17 | 2634510 | -0.5 | 17 | 2631194 | |
| 20 | 2628064 | -0.8 | 19 | 2623687 | |
| 22 | 2633645 | -0.6 | 21 | 2630006 | |
| 24 | 2634786 | -0.5 | 24 | | |
| 27 | 2634814 | -0.5 | 26 | | |
| 29 | 2634183 | -0.5 | 28 | | |
| 32 | 2635942 | -0.5 | 31 | | |

**Data Interpretation:**

From the above results, it can be concluded that the Standard preparation is stable for 32 Hours at 25°C (%Difference is -0.5%), Sample preparation is stable up to 31 Hours at 25°C (%Difference is -0.2).

**5.8.2.7 LINEARITY:**

The linearity of an analytical method is its ability to elicit test results that are directly or by a well-defined mathematical transformation, proportional to the concentration of analyte in samples within a given range.

Performed the linearity with Linezolid standard in the range of 50 to 150% of specification limit.

Recorded the area response for each level and calculated slope, intercept & correlation coefficient. Tested the intercept for statistical equivalence to zero.

Plotted a graph of Linezolid concentration (ppm) on X-axis and Area response on Y -axis.

**Table No.:13. Linearity Details**

| Level | Concentration in ppm | Area Response |
|---|---|---|
| 0 | 0.0000 | 0 |
| 1 | 39.2117 | 1243904 |
| 2 | 47.0540 | 1525990 |
| 3 | 56.8569 | 1768033 |
| 4 | 64.6992 | 2034005 |
| 5 | 72.5416 | 2271984 |
| 6 | 80.3839 | 2511890 |
| 7 | 88.2262 | 2757541 |
| 8 | 96.0685 | 3049760 |
| 9 | 103.9109 | 3313608 |
| 10 | 119.5955 | 3824363 |
| Correlation coefficient | | 1.000 |
| Regression coefficient | | 0.999 |
| Slope | | 31786.712 |
| Intercept | | -11686.235 |
| % Intercept | | -0.5 |

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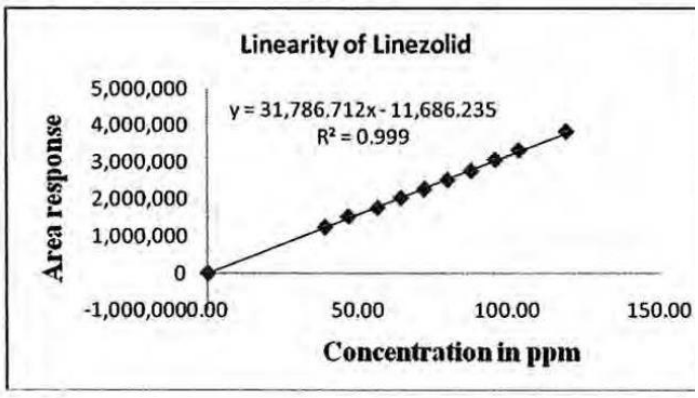


**Fig No.: 2. Linearity graphical representation**

**ACCURACY:**

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value (standard value).

Spiked known quantity of Linezolid standard at 50%, 80%, 100%, 120% and 150% of Assay specification limits into the placebo.

Performed precision at the lowest and the highest levels and for the other levels prepared in triplicate and injected in duplicate for all levels. Calculated the % recovery from the results of Accuracy.

**Table No.: 14:** Recovery of Linezolid:

| % Level (about) | Sample | Mean Area Response | *mg/mL Added | *mg/mL Recovered | % Recovery | Mean % Recovery | %RSD |
|---|---|---|---|---|---|---|---|
| 50 | 1 | 1240140 | 0.0392 | 0.0384 | 98.0 | 98.0 | 0.1 |
| | 2 | 1240095 | | 0.0384 | 98.0 | | |
| | 3 | 1243129 | | 0.0385 | 98.2 | | |
| | 4 | 1239626 | | 0.0384 | 98.0 | | |
| | 5 | 1239616 | | 0.0384 | 98.0 | | |
| | 6 | 1240746 | | 0.0384 | 98.0 | | |
| 100 | 1 | 2505096 | 0.0784 | 0.0776 | 99.0 | 98.9 | 0.2 |
| | 2 | 2501077 | | 0.0774 | 98.7 | | |
| | 3 | 2502763 | | 0.0775 | 98.9 | | |
| 150 | 1 | 3806360 | 0.1176 | 0.1178 | 100.2 | 100.4 | 0.1 |
| | 2 | 3815696 | | 0.1181 | 100.4 | | |
| | 3 | 3821258 | | 0.1183 | 100.6 | | |
| | 4 | 3811428 | | 0.1180 | 100.3 | | |
| | 5 | 3817426 | | 0.1182 | 100.5 | | |
| | 6 | 3811600 | | 0.1180 | 100.3 | | |

**Data Interpretation:**

From the above results, it can be concluded that the recovery is well within the limit. Hence the Method is accurate.

RANGE:

The range of analytical method is the interval between the upper and lower levels of analyte that has been demonstrated to be determined with a suitable accuracy and linearity. Derived the specified range from the Linearity and Accuracy studies.

Acceptance criteria:

The %RSD obtained for all accuracy level determinations should be NMT 2.0. The Correlation coefficient should be NL T 0.998 for Linearity and Accuracy level determinations.

**RESULTS**:

**Table No.: 15:** Linearity Range of Linezolid:

| % Level | Concentration in ppm | Mean Area response |
|---|---|---|
| 50 | 39.2117 | 1243904 |
| 100 | 80.3839 | 2511890 |
| 150 | 119.5955 | 3824363 |
| | Correlation coefficient | 1.000 |

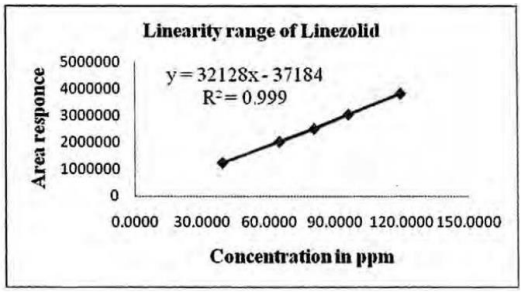


**Fig No.3: Linearity range graphical representation**

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**Table No.: 16:** Accuracy Range of Linezolid:

| Accuracy Range in Linezolid | | |
|---|---|---|
| % Level | Mcg/mL added | Mcg/mL recovered |
| 50 | 0.0392 | 0.0384 |
| 100 | 0.0784 | 0.0775 |
| 150 | 0.1176 | 0.1181 |
| | Correlation coefficient | 1.000 |
| | %RSD | 1.0 |

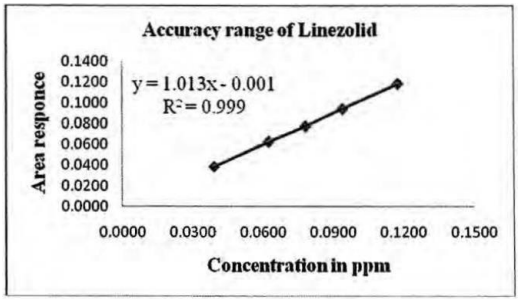


**Fig No.4: Accuracy range graphical representation**

**Data Interpretation:**

From the above results, it can be concluded that the Range of the method is from 50% to 150% of target concentration for Linezolid.

**ROBUSTNESS:**

The robustness of an analytical method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

**Robustness parameters:**

Change in column oven temperature ± 5°C.

Change in flow rate ± 0.2 mL/min.

Change the organic phase ratio± 5.0 %

**Acceptance criteria:**

The System suitability parameters should pass for all the conditions.

**Table No.17: Robustness parameter Details**

| System suitability Parameter | | %RSD for Area | Theoretical plates | Tailing factor |
|---|---|---|---|---|
| Limit | | NMT 2.0 | NLT 1500 | NMT 2.0 |
| Original conditions | | 0.1 | 10286 | 1.2 |
| Flow rate | 1.2 mL/min | 0.0 | 9213 | 1.2 |
| | 0.8 mL/min | 0.1 | 11423 | 1.2 |
| Column Temperature | 30°C | 0.1 | 10795 | 1.2 |
| | 20°C | 0.1 | 9680 | 1.2 |
| Organic Phase | +5% | 0.2 | 9938 | 1.2 |
| | -5% | 0.1 | 10065 | 1.2 |

Data Interpretation: From the above results, it can be concluded that the Method is robust.

**CONCLUSION:**

The proposed HPLC method for estimation of Assay of Linezolid in the Linezolid formulation is validated. The method is found to be specific. The method is also stability indicating as evidenced by forced degradation studies. The method is found to be linear in the specified range for Linezolid. Accuracy of this method is established for Linezolid. The method is found to be precise and robust. A system suitability test is established and related parameters are recorded. Hence this method stands validated and can be used for routine and stability analysis.

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