Formulation and Development of Olanzapine Orally Disintegrating Tablets

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ABSTRACT:

In case of psychiatric treatment immediate release of drug from the dosage form is required. In current investigation, Olanzapine an antipsychotic drug was chosen to develop orally disintegrating tablets using wet granulation technique. In preliminary studies tablets were formulated using different subliming agents like Menthol, Camphor, Ammonium bicarbonate and Thymol. Tablets were also formulated using different superdisintegrants viz. sodium starch glycolate, Crospovidone XL, Croscarmellose sodium and resin as a superdisintegrant (Kyron T-314). Polacrilin potassium A11 (2%) exhibited the least disintegration time and higher in vitro drug release as compared to sodium starch glycolate, Crospovidone and Croscarmellose sodium. so polacrilin potassium was selected for further studies. Olanzapine is basic in nature so citric acid was used to enhance the solubility of Olanzapine. A 32 randomized full factorial design was adopted to optimize the variables, The amount of subliming agent, menthol (X1) and the amount of Kyron T-314(X2) were selected as independent variables. The disintegration time and percentage friability (%F) were selected as dependent variables. Batch F9 containing tablet shows good disintegration time, wetting time, friability, Hardness and dissolution profile at 45 mins. Full models and reduced models were derived for the prediction of the response variable, Y. Based on result of multiple linear regression analysis, it was concluded that on increasing the concentration of menthol (X1) and Kyron T-314 (X2) decreases the disintegration time and shows better drug release. The stability study of selected batch was carried out at two different conditions at room temp and at 40+ 2° C / 75% RH for 3 months.

KEY WORDS: Orally disintegrating tablet, olanzapine, wet granulation, menthol, Polacrilin potassium (Kyron T-314)

INTRODUCTION:

The oral disintegrating tablets (ODTs) have gained popularity in recent years as they cause faster disintegration followed by quick dissolution and thus fast onset of action7. Also these tablets are facilitating significant impact on the patient compliance particularly for those have difficulty in swallowing (Dysphagia1), frequent travelers, and motion sickness complications2. This unit solid dosage forms easy to administer for pediatric, geriatric, and institutionalized patients (specially for mentally retarded and psychiatric patients) and provide good stability, accurate dosing, ease in manufacturing, and suitably handle by patients.3,4,5,6 With enhance taste and flavor of ODT formulations "bitter pill" has changed by excellent mouth feel property and increase the acceptability of bitter medications by various groups of patient.

The bioavailability of drugs that are absorbed from mouth, pharynx, and oesophagus8,9 are increased in these approaches because the pregastric absorption of drugs avoid hepatic metabolism, which reduce the dose10. There are many methodologies applied in the manufacture of Orally disintegrating Tablets which include: Freeze-drying, Sublimation, Molding, Spray drying, Mass extrusion, Addition of superdisintegrants and Techniques of Effervescence, Cotton Candy Process, etc.

Olanzapine is an atypical antipsychotic agent, for treatment of both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation,
and psychotic symptoms in dementia. So, in these conditions the quick onset action of drug is highly desirable and Olanzapine is a suitable candidate for ODTs.

**Materials and Methods**

**Materials**

Olanzapine was gifted by Cadila Healthcare Ltd., Ahmedabad. Polacrilin Potassium (KYRON T – 314) was obtained as a gift sample from Corel Pharma Chem, Ahmedabad. Sodium Starch Glycolate, Crospovidone XL, Croscarmellose Sodium were gifted by Maple Biotech, Pune. Menthol, Ammonium bicarbonate, Aspartame, Mannitol were commercially purchased from Astron Chemical, Ahmedabad. Camphor, Thymol, Talc, Magnesium Stearate were commercially purchased from Purvi Enterprise, Ahmedabad.

**Methods**

**Preparation of Olanzapine Tablets:**

**Procedure for Batch A1 to A6 by sublimation method:** Olanzapine and different subliming agents like (Camphor, Menthol, Ammonium bicarbonate and Thymol) with different ratios (8% to 15%), aspartame, and Mannitol were properly mixed using a glass mortar and pestle. Alcoholic solution of PVP (10% w/v) was added to the above mixture in successive quantity just enough to form lumps. The lumpy mass passed through 100# sieve and granules were collected on a stainless steel tray and allow drying at 50°C for 30 mins in tray drier (model). The dried granules were passed through 20# and retained over 40 #sieves. The granules were lubricated with 2% w/w talc and 1% w/w magnesium stearate. The granules ready for compression were converted into tablets using rotary tablet machine (model). The prepared tablets were exposed 60°C for 10 hrs for sublimation of the volatile ingredients from the tablets.

**Procedure for Batch A7 to A11 by addition of superdisintegrants:** Olanzapine, Aspartame, and Mannitol were mixed using a glass mortar and pestle. The alcoholic solution of PVP (10% w/v) was added to the mixture and allowed to form lumps, passed through 100# sieve and wet granules were dried at 50°C for 30 min in tray drier. The dried granules were passed through 20# and retained over 40 #sieves. Different superdisintegrants (Sodium starch glycolate, Croscarmellose sodium Crospovidone XL and KYRON T - 314) were added extragranularly varying concentration from 1% to 3%. Then the granules were lubricated with 2%w/w talc and 1% w/w magnesium stearate prior to compression.

**Evaluation of formulated tablets**

The crushing strength of the tablets was measured using a Pfizer tester. The friability of a sample of 20 preweighed tablets were evaluated by using a roche friabilator (Singhia Scientific Industries, Ambala), rotated at 25rpm for 4 min. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated. For measurement of disintegration time, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted down.

**In-vitro dissolution test:** The release rate of Olanzapine from orally disintegrating tablets was determined by using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle type) (model). The dissolution test was performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 ± 0.5°C and at 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1, 5, 10, 15, 30, 40 and 45 mins interval, subsequently 10ml of fresh dissolution medium was added after each withdrawal. The withdrawal samples were filtered through a 0.45 µ membrane filter by a filtering assembly. The filtrate is evaluated for Absorbance at 259.7nm using a Shimadzu UV-1800 double beam spectrophotometer.

**Full Factorial Design**

A 3² randomized full factorial design was adopted to optimize the variables. In this design two factors were evaluated each at three levels, and experimental trials were performed at all 9 possible combinations. The amounts of subliming agent, menthol (X1) and the amount of KYRON T-314 (X2), were selected as independent variables. The disintegration time and percentage friability were selected as dependent variables.

**Results and discussion:**

Tablet formulations were prepared using different subliming agents like A1 (with camphor 8%), A2 (with menthol 8%), A3 (with menthol 12%), A4 (with menthol 15%), A5 (with ammonium bicarbonate 8%), A6 (with thymol 8%). All tablets were exposed at 60°C for 10 hours for sublimation of volatile ingredient in the formulations. The sublimation causes increase in the porosity of these tablets. Porosity form in all these batches have shown disintegration time ranging from 230-400 sec. Hardness of the tablets were found to be in the range of 4.0-6.0 kg/cm². The friability of these tablets were found to be comparatively high than the standard. Hence it was decided to incorporate colloidal silicon dioxide, extragranularly, at a concentration of 1% to decrease the friability of the tablets. Batches Containing A1, A5, A6 have shown more disintegration time as compared to menthol containing batches (i.e,A2,A3 and A4). Batch A3 has disintegration time of 242 sec and highest drug release of 62.99% at 45 m among all these batches. So, batch A3 (with menthol 12%) was further selected for optimization. The result indicates that concentration dependent disintegration was observed in batches prepared using menthol as a subliming agent. The porous structure is responsible for faster water uptake that causes faster disintegration. The use of subliming agent resulted in increased friability because of increased porosity.

Further the Tablet formulations(from batch A7 to A11) were carried out using different superdisintegrants like sodium starch glycolate (SSG), Crospovidone XL (CXL), Croscarmellose
sodium (CCS) and Polacrilin potassium (KYRON T-314) at different level of concentrations. Hardness of these tablets were found to be in the range of 3.0-5.5 kg/cm². Batches A7, A8, A9, A10, A11 have shown disintegration time of 180sec, 153sec, 70 sec, 160sec, 60sec respectively. Batch A9 and A11 have shown comparatively better drug releases of 78.43% and 80.18% at 45 min than others. The selection for optimizing superdisintegrant and its concentration in the formulations was done based on time taken for disintegration and higher percentage of drug release. So at the lowest level of disintegrant concentration will achieve higher disintegration rate with combination of sublimation technique. Polacrilin potassium2% (batch A11) containing tablets exhibited the least disintegration time and higher in vitro drug release as compared to sodium starch glycolate, Crospovidone and Croscarmellose sodium(table no). As the percentage of release for batch A11 is less than desired hence this batch is further studied for better release profile. To enhance the dissolution of the poor soluble drug olanzapine, physical mixture of citric acid was used and batch containing physical mixture of 12.5% citric acid displayed higher drug release as compared to other batches.

**Factorial design:**

The amount of subliming agent (menthol, $X_1$) and the resin as a superdisintegrant (KYRON T - 314, $X_2$) were chosen as independent variables in a $3^2$ full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses, where $Y$ is the dependent variable, $b_i$ is the arithmetic mean response of the 9 runs, and $b_i$ is the estimated coefficient for the factor $X_i$. The main effects ($X_1$ and $X_2$) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms ($X_1X_2$) show how the response changes when 2 factors are simultaneously changed. The polynomial terms ($X_1^2$ and $X_2^2$) are included to investigate nonlinearity. The disintegration time and percentage friability for the 9 batches (F1 to F9) showed a wide variation (ie, 24-178 seconds and 0.125%-0.490%, respectively). The data clearly indicated that the disintegration time and percentage friability values are strongly dependent on the selected independent variables. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). Table 4 and 5 show the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for disintegration time and percentage friability indicate a good fit. The equations may be used to obtain estimates of the response as a small error of variance was noticed in the replicates. The significance test for multiple regression coefficients was performed by applying the F test. A coefficient is significant if the calculated t value is greater than the critical value of t.

\[
Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2, \quad \text{..........................(1)}
\]

**Full and Reduced Model for Disintegration Time:**
The fitted equation for full model relating the response was

\[
Y = 48.11111 - 23.1667X_1 - 52.3333X_2 + 13X_1X_2 + 3.833333X_1^2 + 36.33333X_2^2
\]

The fitted equation for reduced model relating the response was

\[
Y = 50.66667 - 23.1667X_1 - 52.3333X_2 + 13X_1X_2 + 36.33333X_2^2
\]

The significance level of coefficient $b_{11}$ was found to be $P = 0.4551$, hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 4. The coefficients $b_1$, $b_2$, $b_{12}$, and $b_{12}$ were found to be significant at $P < 0.05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient $b_{12}$ contributes significant information for the prediction of disintegration time or not. The results for testing the model in portions are shown in Table. The critical value of $F_{\text{tab}}$ is 10.13 (df = 1, 3) at $P$ value of 0.05.Since the calculated value ($F = 0.507$) is less than the critical value ($F = 10.13$). It may be concluded that the interaction term $b_{12}$ does not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model. The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of either Menthol or Kyron T – 314, a decrease in disintegration time is observed; both the coefficients $b_1$ and $b_2$ bear a negative sign. When higher percentage of menthol is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated. It is obvious that in the presence of higher percentage of superdisintegrant Kyron T – 314, higher degree of wicking is facilitated.

**Full and Reduced Model for Percentage Friability:**
The fitted equation for full model relating the response was

\[
Y = 0.272556 + 0.130333X_1 + -0.0145X_2 + -0.05375X_1X_2 + 0.008667X_1^2 + 0.001167X_2^2
\]

The fitted equation for reduced model relating the response was

\[
Y = 0.279111 + 0.130333X_1 - 0.05375X_1X_2
\]

As the significance level of coefficients $b_2$, $b_{11}$, and $b_{22}$ were found to be greater than P (0.05), hence they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 4.The coefficients $b_2$ and $b_{12}$ were found to be significant at $P < 0.05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients $b_2$, $b_{11}$, and $b_{22}$ contribute significant information for the prediction of disintegration time or not. The results for testing the model in portions are depicted in Table. The critical value of $F_{\text{tab}}$ is 9.28 (df = 3, 3) at $P$ value of 0.05. Since the calculated value ($F = 1.01$) is less than the critical value ($F = 9.28$), it may be concluded that the interaction term and polynomial terms do not contribute significantly to the prediction of disintegration time. Hence, conclusions can be drawn considering the magnitude of the coefficient and the mathematical sign (either positive or negative) it carries. An
increase in the concentration of menthol leads to an increase in friability because the coefficient $b_1$ bears a positive sign. When a higher percentage of menthol is used, more porous tablets are produced, which are mechanically weak.

Stability study of optimized batch was carried out according to accelerated stability study conditions as per ICH guidelines (i.e. $40^\circ \text{C}$ in a humidity chamber having 75% RH). Batch withdrawn after three month shown no drastically change in In-vitro drug release profile (Figure 1). The value of similarity factor is found to be 83.24, which was indicating a good similarity of dissolution profile before and after stability studies.

TABLES:

**Table 1:** tablet formulation and evaluation results of preliminary trials using subliming agents

<table>
<thead>
<tr>
<th>Ingredients (mg/tablet)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>A5</th>
<th>A6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Camphor</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Menthol</td>
<td>-</td>
<td>16</td>
<td>24</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ammonium bicarbonate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Thymol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>Aspartame</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mannitol q.s. to</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Disintegration Time(s)</td>
<td>300</td>
<td>275</td>
<td>242</td>
<td>230</td>
<td>380</td>
<td>400</td>
</tr>
<tr>
<td>Friability(%)</td>
<td>0.671</td>
<td>0.648</td>
<td>0.856</td>
<td>0.921</td>
<td>0.592</td>
<td>0.597</td>
</tr>
</tbody>
</table>

All batches contained 10mg olanzapine, 4mg aspartame, 2mg collidon silicon dioxide, 10% PVP in ethanol as a binder, 2% magnesium stearate, 1% talc, 12.5% citric acid as a solubilizing agent and mannitol q.s. up to 200 mg. X1 is the amount of menthol, where $X_1=12mg, 0=16mg$ and $X_1=20mg$; X2 is the amount of Kyron T-314, where $X_2=0=2mg$ and $X_2=4mg$. DT indicates disintegration time and F, friability.

**Table 2:** Tablet formulation and evaluation results of preliminary trials using superdisintegrants

<table>
<thead>
<tr>
<th>Ingredients (mg/tablet)</th>
<th>A7</th>
<th>A8</th>
<th>A9</th>
<th>A10</th>
<th>A11</th>
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<tr>
<td>Olanzapine</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crospovidone XL</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kyron T-314</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Aspartame</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mannitol q.s. to</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Disintegration Time(s)</td>
<td>180</td>
<td>153</td>
<td>70</td>
<td>160</td>
<td>60</td>
</tr>
<tr>
<td>Friability(%)</td>
<td>0.215</td>
<td>0.356</td>
<td>0.346</td>
<td>0.235</td>
<td>0.276</td>
</tr>
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**Table 3:** Formulation and evaluation of batches in full factorial design

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>X1</th>
<th>X2</th>
<th>DT</th>
<th>Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-1</td>
<td>-1</td>
<td>178</td>
<td>0.125</td>
</tr>
<tr>
<td>F2</td>
<td>-1</td>
<td>0</td>
<td>70</td>
<td>0.137</td>
</tr>
<tr>
<td>F3</td>
<td>-1</td>
<td>1</td>
<td>50</td>
<td>0.193</td>
</tr>
<tr>
<td>F4</td>
<td>0</td>
<td>-1</td>
<td>140</td>
<td>0.267</td>
</tr>
<tr>
<td>F5</td>
<td>0</td>
<td>0</td>
<td>47</td>
<td>0.294</td>
</tr>
<tr>
<td>F6</td>
<td>0</td>
<td>1</td>
<td>30</td>
<td>0.259</td>
</tr>
<tr>
<td>F7</td>
<td>1</td>
<td>-1</td>
<td>100</td>
<td>0.49</td>
</tr>
<tr>
<td>F8</td>
<td>1</td>
<td>0</td>
<td>35</td>
<td>0.404</td>
</tr>
<tr>
<td>F9</td>
<td>1</td>
<td>1</td>
<td>24</td>
<td>0.343</td>
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</tbody>
</table>

**Table 4:** Summary of results of regression analysis

<table>
<thead>
<tr>
<th>Response (disintegration time)</th>
<th>b0</th>
<th>b1</th>
<th>b2</th>
<th>b11</th>
<th>b22</th>
<th>b12</th>
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<tbody>
<tr>
<td>FM</td>
<td>48.11111</td>
<td>-23.1667</td>
<td>-52.3333</td>
<td>3.833333</td>
<td>36.33333</td>
<td>13</td>
</tr>
<tr>
<td>RM</td>
<td>50.66667</td>
<td>-23.1667</td>
<td>-52.3333</td>
<td>-</td>
<td>36.33333</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response (Percentage Friability)</th>
<th>b0</th>
<th>b1</th>
<th>b2</th>
<th>b11</th>
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<tbody>
<tr>
<td>FM</td>
<td>0.272556</td>
<td>0.130333</td>
<td>-0.0145</td>
<td>0.008667</td>
<td>0.001167</td>
<td>-0.05375</td>
</tr>
<tr>
<td>RM</td>
<td>0.279111</td>
<td>0.130333</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.05375</td>
</tr>
</tbody>
</table>

* $X_1 =$ MENTHOL and $X_2 =$ KYRON T – 314
**FIGURES:**

![Comparative graph between initial sample & 3 months stability sample of batch F9](image)

**TABLE 5:** Calculations for testing the model

<table>
<thead>
<tr>
<th>Regression</th>
<th>DF</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For Disintegration Time:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>5</td>
<td>22998.44</td>
<td>4599.689</td>
<td>114.5679</td>
<td>0.99479</td>
<td>0.002016</td>
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<tr>
<td>RM</td>
<td>4</td>
<td>22969.06</td>
<td>5742.264</td>
<td>153.2974</td>
<td>0.993519</td>
<td>0.000137</td>
</tr>
<tr>
<td><strong>Error</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>3</td>
<td>120.4444</td>
<td>40.14815</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RM</td>
<td>4</td>
<td>149.8333</td>
<td>37.45833</td>
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<td>-</td>
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</tbody>
</table>

**For Percentage Friability:**

<table>
<thead>
<tr>
<th>Regression</th>
<th>DF</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM</td>
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<td>0.114891</td>
<td>0.022978</td>
<td>49.39695</td>
<td>0.987999</td>
<td>0.000447</td>
</tr>
<tr>
<td>RM</td>
<td>2</td>
<td>0.113477</td>
<td>0.056738</td>
<td>121.1509</td>
<td>0.975836</td>
<td>1.99E-08</td>
</tr>
<tr>
<td><strong>Error</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>RM</td>
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<td>0.000468</td>
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*FM indicates full model; and RM, reduced model
*DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer’s ratio; R², regression coefficient

**REFERENCES:**


