



# KINETIC STUDY OF Fe(II) AND Fe(III) COMPLEXES OF DOPAMINE, (-)-3-(3,4-DIHYDROXYPHENYL)-L-ALANINE AT PHYSIOLOGICAL pH

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The kinetics of complex formation of dopamine, (-)-3-(3,4-dihydroxyphenyl)-L-alanine (Levodopa or LD), with Fe(II) and Fe(III) has been studied spectrophotometrically. The reactions were carried out at a pH range of 3.0 to 9.2, at  $25 \pm 1^\circ\text{C}$ . Complex formation was not observed below pH 4.0. These investigations showed that the Fe(II) and Fe(III) complexes have identical spectra, indicative of same oxidation state of iron in these complexes. Fe(III)-LD complexation was studied only in non-buffered media. The reaction was very fast, and hence was studied using stopped flow technique. This reaction shows a linear dependence on [LD]. While, in case of Fe(II) complexation, a saturation pathway is followed. Rate laws have been deduced.

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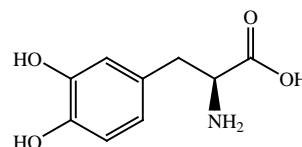
affinity for metal ions, specifically iron, therefore, Levodopa is expected to chelate iron strongly.<sup>15-17</sup> We have studied the effect of pH on stoichiometry and kinetics. Formation constant and reaction mechanism were also evaluated.

## INTRODUCTION

Hemoglobin and myoglobin holds high concentration of iron, which is essential for the oxygen storage and means of transport in the body.<sup>1</sup> Excess iron levels results in enlargement of the liver, cardiac failure, diabetes and Hemochromatosis, a genetic disease, while a major consequence of iron deficiency is Anemia.<sup>2</sup> Ferrous ion ( $\text{Fe}^{\text{II}}$ ), is a vital trace element essential for nearly all creatures.<sup>3</sup> As iron is the most profuse metal for the human body, therefore most symbiosis are tremendously iron dependent. The brain comprises of considerably higher concentration of iron in comparison with other metals.<sup>4</sup> Ferritin mainly exists in the organic form, whilst hemosiderin present in free and reactive form. It is the major iron store in the brain.<sup>5</sup> Due to the presence of BBB (Blood Brain Barrier), iron crosses the endothelial cells and enters in the brain. Therefore, it *cannot* receive iron direct from the blood circulatory system.<sup>6</sup> Accumulation of iron, promotes Alzheimer disease, Hemochromatosis and Parkinson's Diseases (PD), as well.<sup>7-10</sup>

Parkinsonism is caused by deficiency of dopamine in the brain, which might lead to the death of neurons, responsible for production of dopamine in the substantia nigra (SNpc).<sup>11</sup> Deficiency of dopamine in the striatum lead to slow death of Dopaminergic neurons in a progressive way that decrease the capability to organize voluntary movement by the brain.<sup>12</sup>

Keeping in view the role of iron in PD, the present work was planned to evaluate the importance of Fe-LD interaction in this disease. Iron plays a fundamental role as a source for PD, that also supported by pharmacological facts. Number of iron chelators, have been revealed to scale down the intensity of symptoms of PD in patient.<sup>13-14</sup> Levodopa is (-)-3-(3,4-dihydroxyphenyl)-L-alanine, (Figure 1) is an alanine derivative, containing catechol moiety. Catechol has high



**Figure 1.** (-)-3-(3,4-Dihydroxyphenyl)-L-alanine commonly known as Levodopa.

## EXPERIMENTAL

Analytical grade reagents were used in all the experiments. Iron salts ( $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and  $(\text{NH}_4)_2\text{Fe}(\text{SO}_4)_2 \cdot 6\text{H}_2\text{O}$ ) were of Merck and Levodopa was obtained from Wild Wind. Stock and sample solutions were prepared in  $\text{CO}_2$  free distilled deionized water.

### Preparation of metal, ligand and buffer Solutions:

Accurate weight of Fe(II) and Fe(III) salts were dissolved in 100 mL volumetric flask, by using DDI water, to prepare solutions of desired concentration. To make buffers of pH 3.0, 4.0, 4.5, 5.0, 5.5 and 6.0, 100 mL of 1.0 M standardized NaOH solution was taken, its pH was altered by adding varying volumes of 1 M  $\text{CH}_3\text{COOH}$  to get the desired buffer value. Final volume was made up to 1 L with Deionized distilled water, ionic strength ( $\mu$ ) of 0.1 M of all buffer solutions were maintained. The buffer solutions of pH 7.4 and 9.2 were prepared by 2.0 M solution of Tris Base, with the ionic strength of 0.1 M.

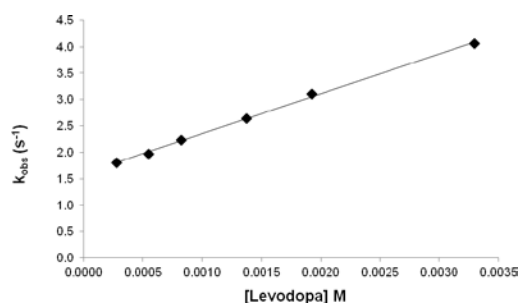
### Kinetic measurements

The temperature was maintained at  $25 \pm 1^\circ\text{C}$ , throughout the experiment. All experiments were carried out in triplicate. Concentration of the metal ion was kept constant throughout the experiments, whereas that of the ligand was

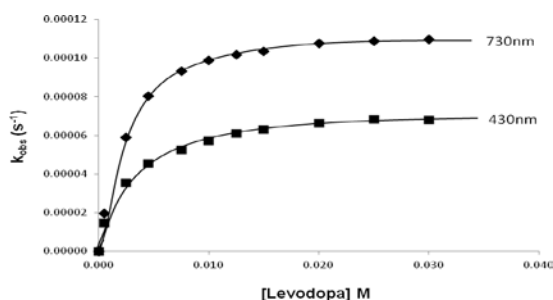
kept from 1:1 to 100 folds, in order to get pseudo first order conditions. Flasks were plugged with stopper, mixed well and analyzed on Genesys 6 Thermo Electron Conformation for the recording of absorbance at  $\lambda_{\max}$ . The reactions of Fe(III) are extremely fast and were studied on stopped flow apparatus, manufactured by Applied Photo Physics. For machine and user interface, Global Oils Work software used in stopped flow apparatus. Only limited work was carried on Fe(III) because of unavailability of facilities.

## RESULTS AND DISCUSSION

The kinetical curves for complex formation between Fe(III) and Fe(II) in non-buffered media can be seen in Fig. 2 and 3.

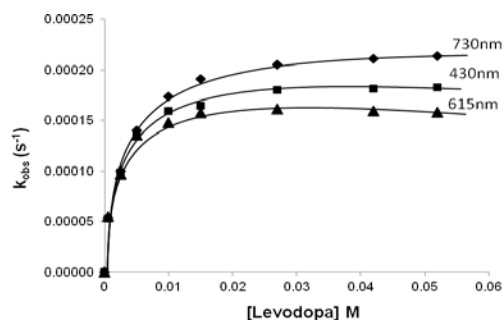


**Figure 2.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(III)-LD in non-buffered medium;  $\lambda_{\max}$  = 730 nm.

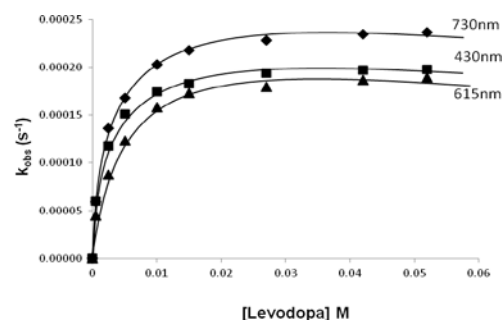


**Figure 3.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD in non-buffered medium.

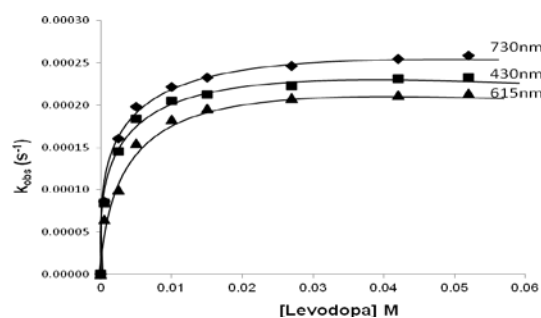
The complex formation reaction between Fe(II) and LD was also studied in non-buffered and buffered media at  $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$ . The corresponding plots of  $k_{obs}$  v/s [LD] at various pH, 4.0, 4.5, 5.0, 5.5, 6.0, 7.4 and 9.2 are given in Figs. 4 to 10, respectively.



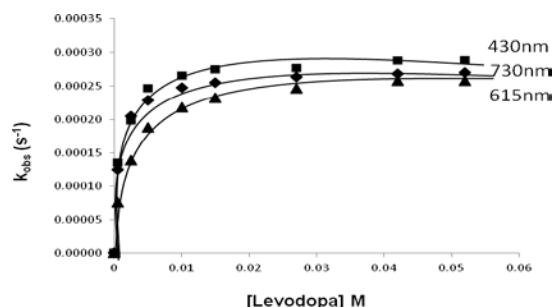
**Figure 4.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD Complex at pH 4.0.



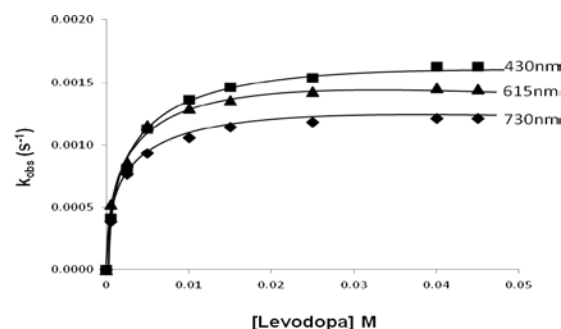
**Figure 5.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD complex at pH 4.5.



**Figure 6.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD complex at pH 5.0.



**Figure 7.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD complex at pH 5.5.

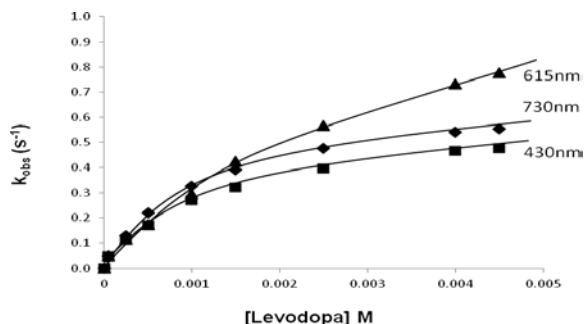


**Figure 8.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD complex at pH 6.0.

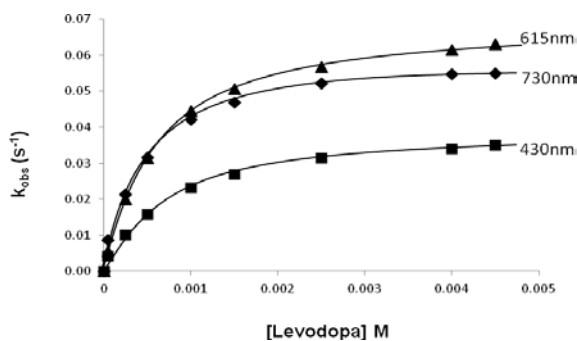
Reactions at pH range 4 to 5.5 were found to be slow, while, those at pH 6, 7.4 and 9.2 were very fast and hence were followed using stopped flow technique.

## Kinetics

The kinetics of formation of Fe(II)-LD and Fe(III)-LD complexes under the experimental conditions were studied spectrophotometrically. These reactions were studied in non-buffered solutions which were further observed under varying conditions of pH, using buffer solutions.



**Figure 9.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD complex at pH 7.0.



**Figure 10.** Plots of  $k_{obs}$  vs [Levodopa] for the formation of Fe(II)-LD complex at pH 9.2.

In the existing experiment  $k_{obs}$  values were evaluated from the slopes of plots of  $\ln |A_t - A_\infty|$  vs time. The kinetic results were fit to the eqn (1).

$$\ln[A_t - A_\infty] = e^{k_{obs} \times t} \quad (1)$$

The experimental rate constants reported here, are the average of three runs.  $k_{obs}$  versus ligand concentration plots showed hyperbolic and linear relationship, in different cases depending on the oxidation state of the metal. These linear and hyperbolic curves, indicated saturation and non-saturation behaviour with respect to the concentration of ligand in the sample. In the case of Fe(II), the hyperbolic dependence of  $k_{obs}$  on the [LD] suggests two pathways of the reaction, while in Fe(III) a linear pathway was observed.

### Fe(III)-LD complex in aqueous (non-buffered) medium

The sample analysis was performed on Stopped-flow machine which was attached with the UV-visible spectrophotometer. The reason to choose this technique is

because the reactions were founded very fast and accomplished within millisecond time scale.

The plot of the  $k_{obs}$  values vs. [LD], at 730 nm is presented in Fig 2. The nonzero intercept and the linearity in the plot are indicative of two term rate law for the reaction of complex formation.

$$k_{obs} = k_0 + k [LD] \quad (2)$$

where

$k_0$  indicates the rate constant for the independent pathway,<sup>[3]</sup> while

$k'$  is the rate constant for the pathway that depends upon [LD].

Values of  $k_0$  were compared with  $k$  and were found to be negligible.

$$k_0 \ll k$$

As the values of  $k_0$  are insignificant they may be taken as negligible. Therefore, it is concluded that,

$$k_{obs} = k [LD] \quad (3)$$

and

$$\text{Rate} = k_{obs} [\text{Fe(III)}] \quad (4)$$

### Fe(II)-LD complex in non-buffered medium

Formation kinetics of Fe(II)-LD in aqueous solution was examined at  $25 \pm 1$  °C. Hyperbolic relationship was observed between  $k_{obs}$  and [L], which is followed by Eqn (4).

$$k_{obs} = \frac{k'[L]}{1+k''[L]} \quad (4)$$

where [L] denotes the concentration of ligand, LD.

In this model parameter  $k'$  represents the 2<sup>nd</sup> order rate constant,  $k''$  defines the approach to saturation and has the units of equilibrium constant. The  $k_{max}$  is evaluated by the ratio of  $k'/k''$ .  $k_{obs}$  is equal to  $k_{max}$ , when the rate approaches a plateau as a function of ligand saturation, while at low ligand concentrations it is equal to  $k'$ . Overlay plot of  $k_{obs}$  values for the Fe(II)-LD is given in Fig. 8.

### Fe(II)-LD complex in buffered medium pH 4.0 to 9.2

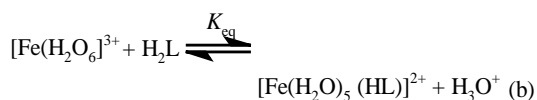
Kinetic parameters were calculated for Fe(II)-LD and the plots of  $k_{obs}$  vs. [LD], at pH span of 4.0 to 9.2, are shown in figure 4 to 10, at 430 nm, 615 nm and 730 nm. These plots are indicative of saturation kinetics with the reverence to [LD]. Fitting of the data to equation 4 gave the values of  $k$ ,  $k'$  and  $k''$  (Table 1).

**Table 1.** Kinetic parameters for the reaction of Fe(II) and Fe(III) with LD.

| Fe(III)-LD at 730 nm |                |                |                |          |            |
|----------------------|----------------|----------------|----------------|----------|------------|
| Medium               | R <sup>2</sup> | Sum of squares | k <sub>o</sub> | k        |            |
|                      | 0.998453       | 5.48E-03       | 1.60           | 7.55E+02 |            |
| Fe(II)-LD at 430 nm  |                |                |                |          |            |
| Medium               | R <sup>2</sup> | Sum of squares | k'             | k''      | k = k'/k'' |
| Aqueous              | 0.996307       | 1.93E-11       | 2.68E-02       | 3.60E+02 | 7.45E-05   |
| pH 4.0               | 0.991805       | 2.77E-10       | 9.98E-02       | 5.29E+02 | 1.89E-04   |
| pH 4.5               | 0.994929       | 1.99E-10       | 1.28E-01       | 6.30E+02 | 2.03E-04   |
| pH 5.0               | 0.990621       | 4.74E-10       | 1.94E-01       | 8.37E+02 | 2.32E-04   |
| pH 5.5               | 0.986697       | 9.88E-10       | 4.00E-01       | 1.40E+03 | 2.85E-04   |
| pH 6.0               | 0.993128       | 1.86E-08       | 7.06E-01       | 4.16E+02 | 1.70E-03   |
| pH 7.4               | 0.995255       | 8.65E-04       | 4.88E+2        | 8.10E+02 | 6.02E-01   |
| pH 9.2               | 0.997760       | 3.07E-06       | 5.33E+1        | 1.312E+3 | 4.06E-02   |
| Fe(II)-LD at 615 nm  |                |                |                |          |            |
| pH 4.0               | 0.988901       | 2.92E-10       | 1.29E-01       | 7.77E+02 | 1.66E-04   |
| pH 4.5               | 0.991773       | 3.10E-10       | 7.14E-02       | 3.58E+02 | 2.00E-04   |
| pH 5.0               | 0.980497       | 9.12E-10       | 9.85E-02       | 4.41E+02 | 2.24E-04   |
| pH 5.5               | 0.990313       | 6.37E-10       | 1.38E-01       | 5.22E+02 | 2.64E-04   |
| pH 6.0               | 0.987146       | 2.63E-08       | 1.99E+00       | 7.43E+02 | 2.68E-03   |
| pH 7.4               | 0.997066       | 1.61E-03       | 4.02E+02       | 2.98E+02 | 1.35E+00   |
| pH 9.2               | 0.999767       | 1.07E-06       | 1.13E+02       | 1.58E+03 | 7.15E-02   |
| Fe(II)-LD at 730 nm  |                |                |                |          |            |
| Aqueous              | 0.998427       | 2.28E-11       | 5.04E-02       | 4.18E+02 | 1.20E-04   |
| pH 4.0               | 0.990804       | 4.33E-10       | 8.11E-02       | 3.62E+02 | 2.24E-04   |
| pH 4.5               | 0.997425       | 1.48E-10       | 1.25E-01       | 5.10E+02 | 2.44E-04   |
| pH 5.0               | 0.992513       | 4.68E-10       | 1.94E-01       | 7.53E+02 | 2.57E-04   |
| pH 5.5               | 0.995616       | 2.84E-10       | 4.14E-01       | 1.55E+03 | 2.67E-04   |
| pH 6.0               | 0.995353       | 6.73E-09       | 8.65E-01       | 6.99E+02 | 1.24E-03   |
| pH 7.4               | 0.998615       | 3.49E-04       | 6.33E+02       | 9.25E+02 | 6.84E-01   |
| pH 9.2               | 0.997923       | 7.04E-06       | 1.38E+02       | 2.27E+03 | 6.07E-02   |

### Proposed mechanism for saturation pathway of Fe(II)-LD chelation

On the basis of observations and fitting of the data to specified equations, following mechanism can be proposed for saturation pathway.



$$\text{Rate} = \frac{d[\text{Fe}(\text{L})_n^{+1}]}{dt} = k_1[\text{FeL}]^{1+} \quad (5)$$

as we know that

$$K_{\text{eq}} = \frac{[\text{FeL}]^{1+}}{[\text{Fe}^{3+}][\text{L}^{2-}]} \quad (6)$$

$$[\text{Fe}^{3+}]_{\text{T}} = [\text{Fe}^{3+}] + [\text{FeL}]^{1+} \quad (7)$$

$$[\text{Fe}^{3+}] = [\text{Fe}^{3+}]_{\text{T}} - [\text{FeL}]^{1+} \quad (8)$$

$$[\text{FeL}]^{1+} = K_{\text{eq}} [\text{Fe}^{3+}]_{\text{T}} [\text{L}^{2-}] - K_{\text{eq}} [\text{FeL}]^{1+} [\text{L}^{2-}]$$

$$[\text{FeL}]^{1+} + K_{\text{eq}} [\text{FeL}]^{1+} [\text{L}^{2-}] = K_{\text{eq}} [\text{Fe}^{3+}]_{\text{T}} [\text{L}^{2-}]$$

$$[\text{FeL}]^{1+} (1 + K_{\text{eq}} [\text{L}^{2-}]) = K_{\text{eq}} [\text{Fe}^{3+}]_{\text{T}} [\text{L}^{2-}]$$

$$[\text{FeL}]^{1+} = \frac{K_{\text{eq}} [\text{Fe}^{3+}]_{\text{T}} [\text{L}^{2-}]}{1 + K_{\text{eq}} [\text{L}^{2-}]} \quad (9)$$

$$\text{Rate} = k [\text{FeL}]^{1+}$$

$$\text{Rate} = \frac{k \times K_{\text{eq}} [\text{Fe}^{3+}]_{\text{T}} [\text{L}^{2-}]}{1 + K_{\text{eq}} [\text{L}^{2-}]} \quad (10)$$

$$\text{Rate} = k_{\text{obs}} [\text{Fe}^{3+}]_{\text{T}}$$

$$k_{\text{obs}} = \frac{k \times K_{\text{eq}}[\text{L}^2]}{1 + K_{\text{eq}}[\text{L}^2]} \quad (11)$$

Final rate law is eqn. (12).

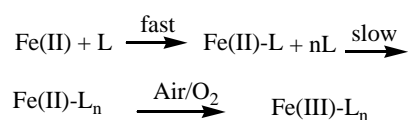
$$\text{Rate} = \frac{k \times K_{\text{eq}}[\text{L}^2] \times [\text{Fe}^{3+}]}{1 + K_{\text{eq}}[\text{L}^2]} \quad (12)$$

We have assumed that  $k \times K_{\text{eq}} = k'$  and  $K_{\text{eq}} = k''$ .

So,  $k = k'/k''$ .

### Effect of pH

Water exchange rate constant of  $\text{Fe}(\text{H}_2\text{O})_6^{2+}$  is  $4.4 \times 10^6$ , and that of  $\text{Fe}(\text{H}_2\text{O})_6^{3+}$  is  $1.6 \times 10^2$ .<sup>18</sup> As the  $\text{H}_2\text{O}$  exchange in  $\text{Fe}^{2+}(\text{aq})$  is 10,000 times faster than  $\text{Fe}^{3+}(\text{aq})$ , our results are in good agreement with this literature value, when the complexation reaction is carried, starting with  $\text{Fe}^{3+}$ . When  $\text{Fe}^{2+}$  was used as metal ion source, the reaction was found to be  $10^{10}$  times slower. The reason for this observation might be multistep reaction, involving oxidation of  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , which is catalyzed by the presence of LD. As  $\text{Fe}^{3+}$ , a  $d^5$  system is inert for substitution, the preferred reaction should be as follows.



On the other hand,  $d^5$  system has low CFAE, and is highly inert regardless of nature of ligand. However,  $d^6$  with strong field is extremely inert. The coordination of 1<sup>st</sup> LD molecule with  $\text{Fe}^{2+}$  might make it highly inert and therefore, the further reaction slows down unexpectedly. LD exhibits LMCT bands only when it is coordinated with higher oxidation states of metal ion. Hence, the complex formation with  $\text{Fe}^{3+}$  would be preferred in this case.<sup>19-20</sup>

The reaction was studied at various pH values and the data presented here shows that the saturation pathway is important at higher pH. At pH 6.0 the reaction is too fast. At pH 7.4 and 9.2 again the same path is followed and the values of rate constants are higher than at lower pH.

This is well documented that the iron LD complexation process is highly pH dependent and lowering the pH would cause a slower rate of reaction. Iron complex formation with LD is prohibited in highly acidic media where  $\text{pH} < 4.0$ .<sup>21</sup>

A significant change in the values of  $k_{\text{obs}}$  in the experimental concentration range of LD, suggests that pH is the main trigger for iron complexation process and the data suggests that the chelation process is also following saturation pathway in the case of Fe(II). We can conclude here that the first-order pathway is dominating over the saturation pathway.

### Effect of pH on the value of $k_{\text{obs}}$ at different $\lambda_{\text{max}}$

According to the values of  $k_{\text{obs}}$  given in the Table 1, the following order at different wavelengths was observed.

The calculated values for kinetic parameters for chelation of Fe(II) with LD at pH 4.0, 4.5 and 5.0, are in the order of  $615 \text{ nm} < 430 \text{ nm} < 730 \text{ nm}$ , while at pH 5.5, the sequence was changed to  $615 \text{ nm} < 730 \text{ nm} < 430 \text{ nm}$ . It is observed in Fig. 8, that peak shifting is very clear at pH 6.0. Values at 730 nm, decrease in contrast to the values at 615 nm and 430 nm, and stands as  $730 \text{ nm} < 615 \text{ nm} < 430 \text{ nm}$ . The trend of the  $k_{\text{obs}}$  values for Fe(II)-LD chelation under the provided conditions, are exactly reverse of the one observed at pH 5.5,  $430 \text{ nm} < 730 \text{ nm} < 615 \text{ nm}$ .

### Statistical proof of the pH dependence of $k_{\text{obs}}$

The SigmaPlot™ Ver. 12.0 statistical software was employed to determine the statistics i.e. significant difference of the kinetic data of Fe<sup>II</sup>-LD complex at different pH and different wavelengths using the One Way ANOVA and Pair *t*-test method.

One Way ANOVA: One Way ANOVA ( $P < 0.050$ ) at SigmaPlot™ software is applied for  $k_{\text{obs}}$  values. Outcome of such statistics is that at different pH all wavelengths (430, 615 and 730 nm) are significantly different. It reflects that with increase or change in pH (4.0 to 9.2) at each wavelength  $k_{\text{obs}}$  values are not agreed with each other. The result verifies that the Fe(II)-LD complexation is pH dependent.

One way ANOVA for the set of all  $k_{\text{obs}}$  values at different wavelength at particular pH, shows overall results ( $p < 0.050$ ) of no significant difference among the kinetics data at all three wavelengths.

Pair *t*-test: The Pair *t*-test was applied on the same set of all pH data at particular wavelengths. The overall result of such statistics ( $P < 0.050$ ) also shows the same significant difference reconfirming the pH dependency of the reaction.

The data of all three wavelengths at respective pH were also evaluated by Student's 't' test. The results of statistics ( $P < 0.050$ ) show no significant difference among the kinetics of different wavelength at same pH. This consequence proves the same reaction was measured on different wavelengths at respective pH.

### CONCLUSION

No complexation was detected below pH 4.5. This is another point of evidence for the existence of Fe in complexes in +3 oxidation state (Fe at low pH exists in  $\text{Fe}^{+2}$  form and is not oxidized).

Formation of complex at pH 4 or higher suggests that no interaction between metal and ligand takes place in stomach, but as the ligand moves through the blood the complexation with body iron becomes important. This interaction may lead to anemia.

Complexation at pH 9.2 shows that Fe-LD complexes might exist in brain because Parkinson's disease is also characterized by iron overload in the brain and the deficiency of Dopamine can be a consequence of excess amounts of iron in brain.<sup>7-10</sup>

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