INTRODUCTION

An increasing in commercial and clinical importance of the therapeutic applications and uses of metal complexes have been reported. Many literature articles gave evidence to the developing significance of the discipline [1-11]. Several chelating agents used clinically may create in most pharmacopoeia [12], while other new one still being sought [13]. Due to Cu(II) free ion toxicity, many medical problems can be improved, such as using of chelating agents in treatment of Wilson’s disease [14].

In order to deactivate a metalloenzyme, a wide study on metalloproteinases environment embodies a survey to design a drug from small organic ligands [15,16]. Enzymes containing zinc is related with various ailments like cancer and arthritis. Therefore, drug improvement approach is reasonable for zinc active site inhibition. Actually, because of the catalytic roles in enzymes and the diversity of enzymatic zinc structure, it considers an attractive target [17,18]. The best known example of a small molecule metal-containing drug is cisplatin, chemically \( \text{cis} \)-\([\text{PtCl}_2(\text{NH}_3)_2]\). Because both Pt\(^{2+}\) and Pd\(^{2+}\) are soft Lewis acids, they prefer donors containing sulfur and nitrogen to make stronger bonds than donors containing oxygen atoms. In terms of acid dissociation constants and complex formation, Pt(II) and Pd(II) complexes perform in the identical way. Nevertheless the fact that Pt(II) complexes are less faster than the corresponding Pd(II) complexes by 10\(^3\) to 10\(^5\) times. This property illuminated the high toxicity of \( \text{cis}-\text{Pd(DACH)}_2\text{Cl}_2 \) and \( \text{cis}-\text{Pd(en)Cl}_2 \) when compared to the analogous Pt(II) complexes, along with their lower antitumor activity [19]. Generally, the medicinal applications of Pd(II) complexes is less. As \(^{103}\)Pd is a radioactive isotope, it can be used as an inhibition for the growing high-grade prostate cancer [20,21]. Conversely, Das and Livingstone suggested that the best activity of N, Pd(II) and S atoms as antitumor agents can be achieved by chelating with inert ligands such as nitrogen and sulfur [22]. They have the suitable liability to transport the metal to the target (DNA) and permit the metal to interact with it. The activity of both tetracycline and Pd(II)-tetracycline complex drug as an inhibitor for growing of two \( E. \ coli \) sensitive bacterial strains are almost similar to each other. While this activity is 16 times more powerful against \( E. \ coli \) HB101/pBR322, which is resistant to tetracycline [23]. Increasing the importance of the ternary complexes, it is believed worthy to study these complexes for number of amlodipine and peptides as drug with Pd(II). Fig. 1 showed amlodipine compound, chemically 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-...
1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl 5-methyl ester, which is a second form of the 1,4-dihydropyridine derivative of the proto-typical molecule nifedipine [24]. This compound (amlodipine) can be used in the management of mild-to-moderate essential hypertension and in the treatment of chronic stable angina. In the present study, the formation procedures of [Pd(drug)(H\(_2\)O)]\(^{2+}\) complex with peptides were investigated. The concentration distribution diagram of the several complex species will be estimated.

**EXPERIMENTAL**

Amlodipine, palladium(II) chloride and peptides e.g., glycylglycine, leucylalana-nine, glycylvaline, glycine and glutamine were provided by Sigma-Aldrich without any further purification. Solutions were prepared using double distilled water.

**Synthesis:** [Pd(drug)Cl\(_2\)] was prepared as described before [25]. AgNO\(_3\) (2 equiv.) was stirred with the chloro complex overnight in order to prepare diaqua complex [Pd(drug)(H\(_2\)O)]\(^{2+}\). The AgCl precipitate was filtrated and the filtrate was diluted in a standard volumetric flask to the required volume.

**Potentiometric measurements:** The titrations were carried out for 40 mL solution mixtures at 25 °C with a gentle and mild-to-moderate essential hypertension and in the treatment of chronic stable angina. The stability constant of the Pd(II) complexes and acid dissociation constant for the ligand were evaluated using the constant ionic strength of 0.1 mol/dm\(^3\) NaNO\(_3\) at 25 °C.

**Acid–base equilibria of [Pd(drug)(H\(_2\)O)]\(^{2+}\):** Because the complex [Pd(drug)(H\(_2\)O)]\(^{2+}\) could suffer from hydrolysis [28], the potentiometric records were fitted to numerous acid-base simulations in order to evaluate its acid-base chemistry. The results obtained are shown in Table-1. The program HYSS was used in order to obtain the concentration distribution diagrams [27] with the experimental condition used.

**RESULTS AND DISCUSSION**

The stability constant of the Pd(II) complexes and acid dissociation constant for the ligand were evaluated using the ionic strength of 0.1 mol/dm\(^3\) NaNO\(_3\) at 25 °C.

**Table-1**

<table>
<thead>
<tr>
<th>System</th>
<th>p</th>
<th>q</th>
<th>r</th>
<th>(\log \beta^p)</th>
<th>(pK^n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(drug)-OH</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>-4.48 (0.01)</td>
<td>-</td>
</tr>
<tr>
<td>Glycylglycine</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7.97 (0.00)</td>
<td>5.96</td>
</tr>
<tr>
<td>Leucylalanine</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8.13 (0.02)</td>
<td>6.91</td>
</tr>
<tr>
<td>Glycylvaline</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8.24 (0.01)</td>
<td>6.12</td>
</tr>
<tr>
<td>Glutamine</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8.98 (0.00)</td>
<td>10.45</td>
</tr>
<tr>
<td>Glycinamide</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7.88 (0.00)</td>
<td>4.67</td>
</tr>
</tbody>
</table>

\(p, q, r\) and \(r\) are the stoichiometric coefficient corresponding to Pd (drug), L and H\(^+\) respectively.

\(\beta^p\) and \(pK^n\) are standard deviations given in parentheses.

The distribution diagram for [Pd(drug)(H\(_2\)O)]\(^{2+}\) and its hydrolyzed species is displayed in Fig. 2. The maximum monohydroxo concentration increase as the pH increase, it is reached 51.63 at pH range from 6 to 8, that means they are the key species existing in solution in the physiological pH range. Furthermore, as concentration of monohydroxo species decrease, as pH increase, the main species above a pH of about 10 (10 dihydroxo species) will be increased.

![Fig. 2. Distribution of different species as a function of pH in the hydrolysis of Pd(drug)(H\(_2\)O)\(^{2+}\) system](image-url)
Ternary Pd(II) complexes: The potentiometric records of the Pd(drug) peptide system were fitted by different simulations. The complexes formation with stoichiometric coefficients 110 and 11-1 give a reliable results for the most suitable model. In the 110 case, the peptide is attached through the carbonyl oxygen and amino groups. Coordination of the carbonyl and amino groups will led to form the complexes. A modification of the coordination centers from carbonyl oxygen to amide nitrogen are well predictable and would be happen after deprotonation of the amide group [29].

The peptides leucylalanine, glycylvaline and glycylglycine may coordinate through carbonyl group with the amide group in the side chain and the terminal amino group. The ligands would then act as a simple amino acid. Otherwise, the amide group in the side chain and the terminal amino group, the amide oxygen and amino groups. Coordination of the carbonyl and

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REFERENCES
