Binding mechanism of the antidiabetic drug, metformin with the digestive enzyme, pepsin: An experimental and theoretical study

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Metformin is a frontline drug used to treat diabetes mellitus type-2 and is administered orally to the patients. Pepsin is an important enzyme that primarily functions as digestive enzyme. It is of concern that metformin being an orally administered drug may interact with pepsin and consequently affect its physiological function. This may result into serious side effects like vomiting, nausea etc. Therefore, there is a need to investigate the binding mechanism of metformin with pepsin.

In this study, the binding of metformin with pepsin has been studied using fluorescence spectroscopy, isothermal titration calorimetry (ITC), circular dichroism (CD) spectroscopy and molecular modelling techniques.

Fluorescence results showed that Stern Volmer constants decreased inversely with temperature thus quenching is essentially static in nature. The binding constant value and stoichiometry suggested that binding forces are essentially non-covalent in nature and there is single class of binding sites. The conformational change in pepsin upon binding was confirmed using change in CD spectra of pepsin in different concentrations of metformin. Thermodynamic investigations revealed that the binding of metformin to pepsin was driven essentially by favourable enthalpy and unfavourable entropy and the major driving forces are hydrogen bond and van der Waal forces. Molecular docking suggested that the binding of metformin to pepsin is characterized by a high number of binding sites. Therefore, metformin binds significantly with pepsin.

Keywords: fluorescence quenching; isothermal titration calorimetry; circular dichroism; pepsin; metformin

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