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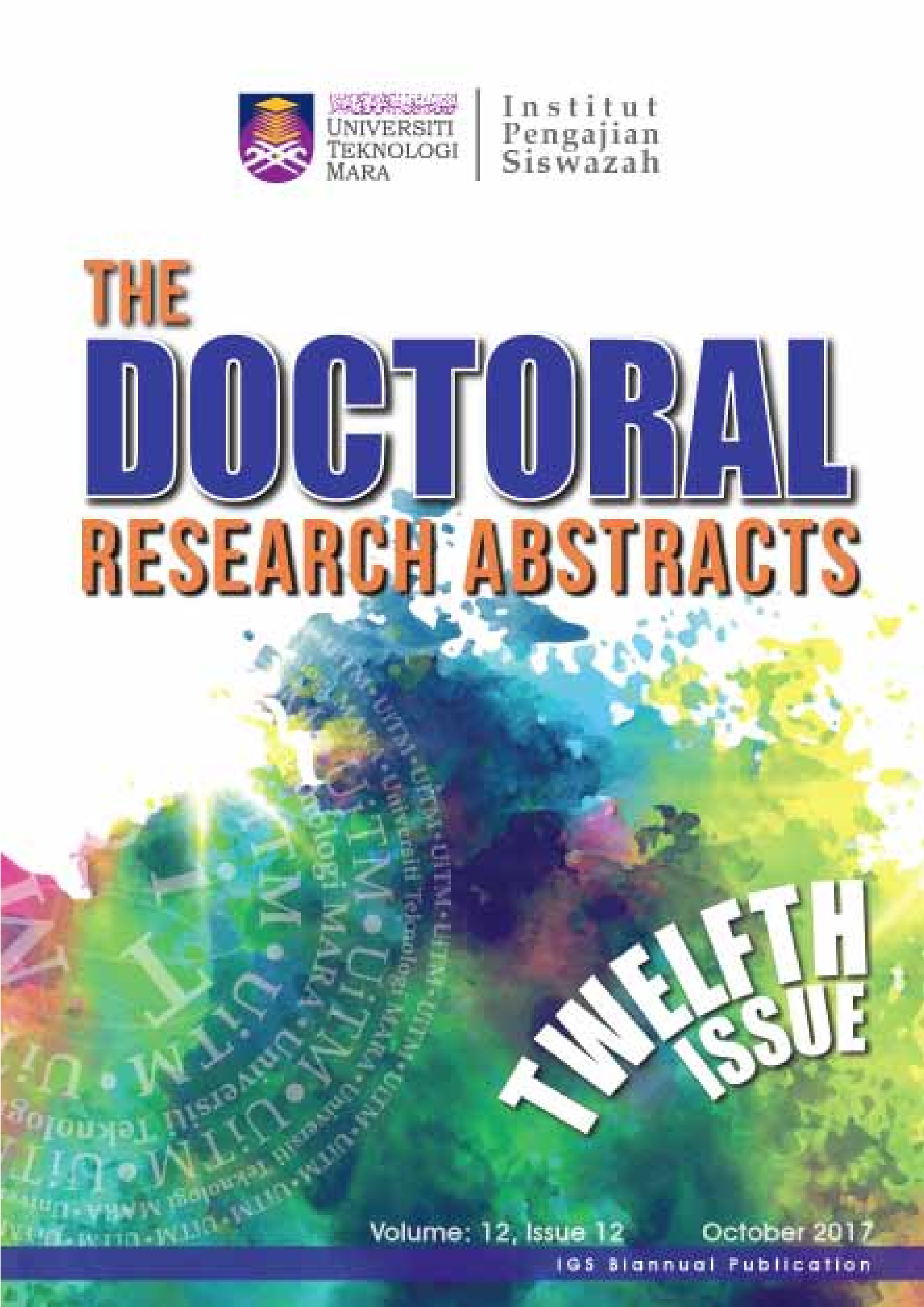
THE DOCTORAL RESEARCH ABSTRACTS



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Name : NIK SALWANI BINTI MD AZMI

Title : ELECTRIC POTENTIAL ASSISTED CRYSTALLIZATION OF LISOLEUCINE IN AQUEOUS PHASE: EXPERIMENTAL AND COMPUTATIONAL MODELLING APPROACH

Supervisor : DR. NORNIZAR ANUAR (MS)
DR. NOOR FITRAH ABU BAKAR (CS)

Crystallization is a major technological process for particle formations. It is important and widely used in the production of pharmaceutical drugs since most drugs particles are produced in crystalline form. L-isoleucine is one of the drugs that exist in crystalline form and it can be produced through crystallization process. However, even slight changes in the crystallization condition can drastically alter crystals properties. Control of the process in order to control the physicochemical properties (solubility, morphology, polymorphism) is crucial to produce the right type of crystal. To overcome this problem, electric potential was applied with the intention to control the process. Hence it has become the main objective of this study to determine the effect of electric potential on solubility and mestastable zone width (MSZW) of L-isoleucine crystallization. Solubility of L-isoleucine experiment was conducted using three different methods; (1) Solubility Method A: Gravimetric method, (2) Solubility Method B: Isothermal dissolution and (3) Solubility Method C: Dissolution with controlled heating rate, while polythermal and isothermal method was adopted for the crystallization process. The results showed that all three methods gave significant difference in solubility data. The inconsistency of the solubility data led to the determination of conductivity of the solution where the presence of aggregation was proven to be present based on the critical aggregation concentration (CAC). Solubility data was also correlated to two different existing mathematical models; modified Wilson model and modified Wilson coupled with Pazuki-Rohani model, in order to assess the suitability of the model to be used for L-isoleucine. Based on the result, modified Wilson coupled with Pazuki-Rohani model was the most suitable model to explain the solubility behaviour of L-isoleucine, with and without the presence of electric potential due to the lower value of root mean square error (RMSE). Polythermal crystallization experiment revealed that the MSZW of the system with the presence of electric potential decreased compared to the MSZW without the presence of electric potential. Nucleation rate was proven to increase when electric potential was applied to the solution. Isothermal crystallization was also investigated with the presence of electric potential. The induction time reduced when the concentration increases and when the electric potential was applied to the solution, meaning that the electric potential promoted the nucleation process so that it can be achieved faster. The nucleation rate was calculated and it was found that for low supersaturation system, the nucleation rate was higher when electric potential was applied to the solution compared to the solution system without the presence of electric potential. Characterization of L-isoleucine product crystal recovered at the end of the experiment using x-ray powder diffraction (XRPD) revealed that mixture of Form A and Form B existed in the solution for polythermal crystallization method while only Form B polymorph existed in the solution for isothermal crystallization. Meanwhile, differential spectroscopy calorimetry (DSC) showed that only Form A existed in the solution for both methods. No proton transfer was observed to occur based on the characterization using Fourier transform infrared (FTIR) as no –COOH functional group was observed in the spectrum. Molecular dynamic simulation was also conducted to find the nucleation rate and compared with the experimental isothermal crystallization data. The simulated nucleation rate was found to be in a degree higher than the experimental data. The critical number of molecules and critical radius was also found to be in a good agreement with the experiment data.