THE DOCTORAL RESEARCH ABSTRACTS

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Conventional fluid-bed and immersion film coating of hydrophilic zinc pectinate spheroids using ethylcellulose-pectin mixture is met with fast drug release due to hydrophobic ethylcellulose coat detachment. This study explored *in situ* intra-capsular spheroid coating for colon-specific delivery of 5-fluorouracil. The solid coating powder was constituted of ethylcellulose and pectin in weight ratios of 11:0 to 2:9. Its weight ratio to spheroids was varied between 2:3 and 3:2. Delayed 5-fluorouracil release was obtained when the weight ratio of ethylcellulose and pectin in coating powder was kept at 8:3, and weight ratio of solid coating powder to spheroids was kept at 3:2 with particle size of ethylcellulose reduced to 22 μm. *In situ* intra-capsular wetting of pectin coat by dissolution medium resulted in the formation of ethylcellulose plug interconnecting with spheroids through the binding action of pectin. The majority of drug was released in the colon.

The incidence of Alzheimer’s disease (AD) is expected to increase exponentially as the population ages. Continuing research in this area is essential to better understand this disease and develop strategies for prevention and treatment. Recent genome-wide association studies have identified several novel loci as genetic risk factors of AD. Previous studies also suggest the total plasma homocysteine (tHcy) level and its biological determinants such as folate and vitamin B₁₂ contribute to the risk of AD. Some of them highlight the correlation between AD risk and genetic polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) and transcobalamin (*TCN II*). The major allele frequencies were measured by allele-specific restriction fragment length polymorphism (RFLP) analysis and allele-specific PCR. By employing a novel allele-specific PCR method, this study investigated the association of the *MTHFR* rs1801133 and *TCN II* rs1801198 polymorphisms and total plasma homocysteine level with the risk of Alzheimer’s disease based on clinical data from the Malaysian population. The study was conducted with the approval of human ethic committees. The study results provide support for the involvement of *MTHFR* and *TCN II* polymorphisms in the development of AD in the Malaysian population.

Faculty of Medicine

A study to evaluate the effects of nicotine and simultaneous supplementation of γ-tocotrienol (γ-TCT), one of the four isomers in tocotrienols (TCT), and nicotine, on *in vitro* and *in vivo* embryonic development in mice (*Mus musculus*) had been carried out. Several approaches were undertaken including an investigation on in vitro effects of various doses and durations of nicotine treatment on pre-implantation embryonic development. Results showed that nicotine treatment decreased the number of retrieved embryos, resulted embryo degeneration, delayed embryo cleavage, induced disproportionate size of blastomeres and degraded blastomeres (p<0.05). Moreover, the deleterious impact of nicotine on pre-implantation embryonic development was dose- and treatment duration-dependent with a corresponding increase in plasma malondialdehyde (MDA) concentrations (p<0.05). Based on this finding, the study was further elucidated in terms of examining the dose-related beneficial effects of γ–TCT in nicotine-induced cessation of pre-implantation embryonic development *in vitro*. Results showed that γ-TCT could prevent the duration- and dose-related toxic effects of nicotine on pre-implantation embryonic development.

The incidence of Alzheimer’s disease (AD) is expected to increase exponentially as the population ages. Continuing research in this area is essential to better understand this disease and develop strategies for prevention and treatment. Recent genome-wide association studies have identified several novel loci as genetic risk factors of AD. Previous studies also suggest the total plasma homocysteine (tHcy) level and its biological determinants such as folate and vitamin B₁₂ contribute to the risk of AD. Some of them highlight the correlation between AD risk and genetic polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) and transcobalamin (*TCN II*). The major allele frequencies were measured by allele-specific restriction fragment length polymorphism (RFLP) analysis and allele-specific PCR. By employing a novel allele-specific PCR method, this study investigated the association of the *MTHFR* rs1801133 and *TCN II* rs1801198 polymorphisms and total plasma homocysteine level with the risk of Alzheimer’s disease based on clinical data from the Malaysian population. The study was conducted with the approval of human ethic committees. The study results provide support for the involvement of *MTHFR* and *TCN II* polymorphisms in the development of AD in the Malaysian population.

* (MS) = Main Supervisor  (CS) = Co Supervisor
region and complete drug release was obtained through digestion of core spheroids by pectinase. Through \textit{in vivo} pharmacokinetic and pharmacodynamic studies, the intra-capsular coated spheroids were found to be able to reduce the drug bioavailability, enhance its accumulation at colon and reduce both number and size of tumor through reforming the tubular epithelium with basement membrane and restricting the expression of cancer from adenoma to adenocarcinoma. Given a dosage regimen of 15 mg/kg/day for 5 days in rats, the intra-capsular coated spheroids also eliminated the formation of aberrant crypt foci which represented a putative preneoplastic lesion in colon cancer, unlike other treatment modes. Inferring hundred-and-twelve cases and a hundred-and-nineteen controls were successfully recruited and analyzed for the selected SNPs and analytes. Cross tabulation analyses and logistic regression were performed in four different models. Genetic analyses showed that \textit{APOE} ε4, \textit{APOE} rs429358, \textit{ABCA7} rs3764650, \textit{MS4A4E} rs670139, \textit{MS4A6A} rs610932, and \textit{CD2AP} rs9349407 were statistically significantly associated with AD risk. The distribution of all selected SNPs was also determined after stratifying all samples by the presence of \textit{APOE} ε4 copy. In the stratified samples, statistically significantly different values were observed only in subjects without \textit{APOE} ε4 copy for \textit{ABCA7} rs3764650 and \textit{MS4A4E} rs670139. The AD risk of a person with GG genotype for \textit{ABCA7} rs3764650 is increased to around 3.7-fold in model I and 5.2-fold in model III. Whereas, the AD risk of a person with AA genotype for \textit{MS4A4E} rs670139 is increased to around 3.3-fold in model I and III. The mean tHcy levels were statistically significantly higher in cases than in controls while the mean serum holotranscobalamin (holoTC) levels were statistically significantly lower in cases than in controls. The logistic regression analysis showed that the \textit{APOE} rs429358 is the main predictor variable. Other significant predictor variables were age at assessment, social class, holoTC, \textit{ABCA7} rs3764650, \textit{MS4A6A} rs610932, folate and LDL. The combination of them significantly predicted 35.8% of variance in the model. The developed method will enable researchers to study AD-related SNPs using an inexpensive method. Our findings show that the significant SNPs may influence the AD risk in the population. It is plausible that the effect of other SNPs on AD risk is specific to certain ethnic group or that effect is not large enough to be identified reliably by a cohort of our size. To the best of our knowledge, this is the first study aimed to determine the potential contribution of the SNPs to AD in a Malaysian population.

deterioration of pre-implantation embryo quality when supplemented simultaneously with nicotine. Moreover, \textit{γ}-TCT of 60 mg/kg bw/day was found to be the optimal effective dose in lowering plasma levels of MDA during pre-implantation embryo development (p<0.05). Findings of \textit{in vitro} study were applied in \textit{in vivo} approach to evaluate the effect of simultaneous supplementation of \textit{γ}-TCT with nicotine on embryo development, blastocyst implantation, foetal growth, length of gestation, foetal outcome and survival rate of the neonates. Results showed that nicotine impaired post-implantation embryo growth and development (p<0.05). Pregnancy outcome and survival of the neonates were also reduced (p<0.05). The rise in oxidant levels reduced the enzymatic antioxidant defense system (p<0.05). Pregnancy-related levels of progesterone (\textit{P}4) and oestrogen (\textit{E}2) were also significantly affected (p<0.05). Through combating nicotine-induced oxidative stress, \textit{γ}-TCT was able to sustain the physiological/normal sequence of blastocyst implantation, foetal growth, pregnancy outcome and survival of the neonates. Moreover, maintenance of pregnancy until term possibly resulted from sustaining the levels of plasma \textit{P}4 and \textit{E}2 as evident in normal pregnancy. In conclusion, \textit{γ}-TCT could be used to minimize nicotine-induced oxidative stress-related deterioration of pre- and post-implantation embryo development, intrauterine foetal growth, pregnancy outcome and survival of the neonates.