UNIVERSITI PUTRA MALAYSIA

CO-PRECIPITATION OF ACETAMINOPHEN AND EUGRAGIT RL 100 USING SUPERCRITICAL ANTI-SOLVENT IN CONTROLLED DRUG DELIVERY

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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September 2009

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The controlled drug release has been proven to enhance the bioavailability of a drug by maintaining the drug concentration in therapeutic level within certain period of time and lowering the risk of drugs side effects by reducing the frequency of drug administration. Among the available drug administration systems, microcapsule has provided advantages over the conventional mode, due to higher efficiency and flexibility. This microcapsule can be produced by supercritical fluids (SCF) method which currently been used in composite particles production. This application solves the limitations of conventional pharmaceutical methods for the production of active ingredient loaded micro particles. Supercritical anti-solvent (SAS) is one of the SCF methods proven to have good potential in micronization of pure component. In this technique, SCF acts as an anti-solvent for the feed solution and the precipitation occurs when these two media (SCF and feed solution) contact each other. Therefore, the general objective of this study is to widen the application of SAS in the co-

precipitation of two components namely acetaminophen in Eudragit RL 100 towards controlling the delivery of the drug.

The investigation began with the development of a mathematical model to estimate the rate of mass transfer between a solvent droplet and CO_2 during SAS process in the supercritical regime. The simulation results show that, the solvent droplet expands when the solvent is denser than CO_2, and shrinks when the CO_2 is denser than the solvent. Both of these phenomena occur in less than one second. Based on the developed mathematical model, SAS system with 490ml of precipitation vessel is designed and developed. The design work focuses on the precipitation vessel, particle collector, temperature control system, process stream and selection of spraying device. After the commissioning of the SAS completed, the system is used to determine the optimum operating conditions for co-precipitation of acetaminophen in Eudragit RL 100. The optimum conditions are determined based on the encapsulation efficiency, particle size, product recovery and loading efficiency. The optimum conditions are 110 bars, 35 °C, 1.75 ml/min feed flow rate and 35 mg/ml polymer concentration.

The repeatability and consistency of the SAS system is also determined to ensure the accuracy of the results. At least 90% consistency is achieved in the co-precipitation of acetaminophen in Eudragit RL100 as judged by the particles size. In addition, the analysis of fourier transform infra red (FTIR) and thermo gravimetric analyzer (TGA) prove that the association between the acetaminophen and Eudragit RL 100 is physical. The results also show that the SAS process do not change the chemical structure (FTIR and high performance liquid chromatography (HPLC)) and thermal

stability (TGA and differential scanning calorimetry (DSC)) of acetaminophen during the process. However, the crystallinity of treated acetaminophen is marginally reduced compared to the untreated acetaminophen (x-ray diffraction (XRD)). More importantly, SAS process has successfully improved the homogenity and size of acetaminophen which is evidenced from the image of scanning electron microscope (SEM). The diffusion coefficient for the release of the processed acetaminophen is also determined by Fick's second law in this study. In is found that the diffusion coefficient is affected by the particle size and polymer concentration. The estimated diffusion coefficient has a magnitude of 10^{-14} m^2/s.

In conclusion, SAS technique has been proven to be one of the promising alternative techniques for co-precipitation of two solutes in drug microcapsules production for controlled drug delivery.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PEMENDAKAN BERSAMA ACETAMINOPHEN DAN EUDRAGIT RL100 DENGAN MENGGUNAKAN ANTI-PELARUT SUPERKRITIKAL DALAM PENGAWALAN PENGHANTARAN UBAT

Oleh

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Pengawalan penghantaran ubat yang telah dibuktikan dalam peningkatan kebolehdapatan-bio ubat dengan mengekalkan kepekatan ubat dalam tahap rawatan pada satu jangka masa dan juga mengurangkan risiko kesan tidak baik daripada ubat kerana mengurangkan frekuensi pengambilan ubat. Antara sistem pengawalan yang sedia ada, mikrokapsul memberi kebaikan seperti memberi kesan yang lebih tinggi dan cara pengambilan yang lebih fleksibel berbanding dengan cara lama. Mikrokapsul ini boleh dihasilkan melalui bendalir superkritikal (SCF) yang merupakan salah satu cara digunakan pada masa sekarang untuk menghasilkan partikel komposit. Cara ini mengatasi kekurangan cara lama yang digunakan di bidang farmaseutikal untuk menghasilkan partikel mikro yang mengandungi ramuan aktif dan ia berkembang dengan pesat dalam bidang penghasilan partikel mikro. Anti-pelarut superkritikal (SAS) adalah satu cara yang telah dibuktikan kegunaannya dalam bidang pengecilan saiz komponen tulen. Dalam cara ini, SCF berfungsi

sebagai anti-pelarut bagi larutan suapan dan pemendakan berlaku apabila dua media ini (SCF dan larutan suapan) bertemu. Justeru, objektif umum pengajian ini adalah untuk memperluaskan kegunaan SAS yang melibatkan dua komponen seperti pemendakan-bersama acetaminophen dalam Eudragit RL 100 untuk pengawalan penghantaran ubat.

Pengajian ini bermula dengan menerbitkan satu model matematik untuk menjangka pemindahan jisim antara titisan pelarut dan CO_2 semasa proses SAS di keadaan superkritikal. Keputusan menunjukkan bahawa titisan pelarut mengembang apabila ketumpatan pelarut adalah lebih tinggi berbanding dengan CO_2, dan titisan pelarut mengecut apabila CO_2 adalah lebih tumpat daripadanya. Walau bagaimanapun, kedua-dua keadaan ini berlaku dalam jangka masa kurang daripada satu saat. Berasaskan daripada keputusan model, satu sistem SAS dengan 490 ml benjana pemendakan telah direka dan dibangun. Ia merangkumi rekaan bejana pemendakan, pengumpul partikel, sistem pengawalan suhu, penyusunan proses dan juga alat penyebaran. Keadaan optimum untuk pemendakan bersama acetaminophen dan Eudragit RL 100 ditentukan setelah sistem SAS itu telah dikenalpasti. Keadaan optimum ini ditentukan berasas daripada kecekapan pengalutan, saiz partikel, pemulihan produk dan kecekapan pengisian. Keadaan optimum yang telah ditentukan ialah:110 bar, 35 °C, 1.75 ml/min kadar suapan and 35 mg/ml kepekatan polimer.

Sistem SAS itu juga mampu mengekalkan sekurang-kurangnya 90% konsistensi dalam pemendakan-bersama acetaminophen dan Eudragit RL 100 berasaskan saiz partikel. Hubungan antara acetaminophen dan Eudragit RL 100 adalah fizikal sahaja

setelah dianalisis oleh *fourier transform infra red* (FTIR) dan *thermo gravimetric analyzer* (TGA). SAP juga dikenalpasti bahawa ia tidak mengubah struktur kimia (FTIR dan *high performance liquid chromatography* (HPLC)) dan kestabilan terhadap haba (TGA dan *differential scanning calorimetry* (DSC)) acetaminophen semasa proses. Akan tetapi, tahap kristal acetaminophen (*x-ray diffraction* (XRD)) telah berkurangan berbanding dengan acetaminophen asal. Proses SAS juga mampu mengecilkan serta menyeratakan saiz acetaminophen yang dilihat bawah *scanning electron microscope* (SEM). Angkali serapan acetaminophen yang telah diproses berjaya ditentukan dengan hukum kedua Fick dalam pengajian ini. Keputusan menunjukan bahawa ia dipengaruhi oleh saiz partikel dan juga kepekatan polimer. Anggaran angkali serapan adalah dalam linkungan 10^{-14} m^2/s.

Kesimpulannya, teknik SAS menunjukkan bahawa ia merupakan cara alternatif untuk pemendakan-bersama dua komponen yang bermatlamat untuk pengawalan penghantaran ubat.

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I certify that an Examination Committee has met on 29 September 2009 to conduct the final examination of Chong Gun Hean on his Doctor of Philosophy thesis entitiled "Co-Precipitation of Acetaminophen and Eugragit RL 100 Using Supercritical Anti-Solvent in Controlled Drug Delivery Application" in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the student be awarded the relevant degree.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Date: 16 November 2009

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

CHONG GUN HEAN

Date:

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LIST OF ABBREVIATIONS

ρ	= Density (kmol/m^3)
ϕ	= Fugacity coefficient
ω	= Acentric factor
θ	= Temperature of CO_2 (°C)
Ψ_v	= Diameter of vessel (mm)
Ψ	= Outside diameter of tubing (m)
ρ_A	= Density of anti-solvent
μ	= Viscosity
σ	= Interfacial tension droplet to surrounding
a, b	= Parameters in Peng-Robinson equation of state
a_m, b_m	= Parameters in Peng-Robinson equation of state of binary mixture
k, l	= Binary interaction parameters
r	= Radial coordinate (m)
t	= Time (s)
$\bar{V}_r$	= Apparent radial velocity (m/s)
v	= Molar volume (m^3/kmol)
v_f	= Superficial velocity of droplet (m/s)
x_A	= Mole fraction of carbon dioxide
u_R	= Relative velocity droplet surrounding
d	= Initial droplet diameter
c	= Specific heat of water (J/Kg °C)
D	= Diffusion coefficient from Fick's law (m^2/s)
D_ϕ	= Thermodynamic correction diffusion coefficient (m^2/s)

D_l^o = Liquid phase diffusion coefficient at infinite dilution (m^2/s)

D_g^o = Gas phase diffusion coefficient at infinite dilution (m^2/s)

N = Mass Flux due to composition gradients (kg/m^2)

L = Length of tubing (m)

Q = Feed flow rate (cm^3/min)

A = Surface area (m^2)

A_c = Cross sectional area of capillary (m^2)

L_v = Length of vessel (mm)

V_v = Volume of vessel (ml)

P_i = Design pressure (N/mm^2)

R_i = Internal radius (mm)

S = Allowable stress of particular material

E = Joint efficiency

C_p = A design constant

D_e = Nominal plate diameter (mm)

N_{We} = Weber number

N_{Re} = Reynolds number

N_{Oh} = Ohnesorge number

M_t = Cumulative amount of drug release at time t

M_∞ = Cumulative amount of drug release at infinite time

P = Pressure (Pa)

P_c = Critical pressure (Pa)

R_o = Initial droplet radius (m)

T = Temperature (K)

T_1 = Inlet temperature (°C)

M = Mass of water (kg)

U = Overall heat transfer ($W/m^2.K$)

T_c = Critical temperature (K)

L = Liquid phase

V = Vapor phase

S = Solid phase

F = Fluid

LST = Lower Solution Temperature

UST = Upper Solution Temperature

SCF = Supercritical Fluid

SCCO2 =Supercritical carbon Dioxide

SAS = Supercritical Anti-Solvent

RESS = Rapid Expansion Supercritical Solution

GAS = Gas Anti-Solvent

DMSO = Dimethyl sulfoxide

ASES = Aerosol Solvent Extraction System

PCA = Precipitation with a Compressed Anti-solvent

SEDS = Solution Enhanced Dispersion by Supercritical fluids

SAS-EM = Supercritical Anti-Solvent with Enhanced Mass transfer.

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CHAPTER 1

INTRODUCTION

1.1 Background

Controlled drug delivery products in the form of composite particles, using biocompatible or biodegradable polymers, have received considerable attention in the recent years. Among the potential applications of these composite particles is the protection of the sensitive therapeutically active molecules against *in vivo* degradation. It may also reduce the toxicity side effects which can occur when some highly active drugs like those used for cancer treatment are administered in the form of a solution. Besides, it helps the patient to be more comfortable by avoiding repetitive injection or reducing the use of perfusion pumps, and may also leads to improvement in favorable drug pharmacokinetics (Gref *et al*., 1995).

The effective use of pharmacologically active substances in the chemotherapy of cancer, viral infections, and many other diseases suffers from non-specific toxicity and poor tissue specificity of drugs. These composite particles can also be used as carriers for targeting these pharmacologically active substances by the intravenous route in order to increase the active substance's effectiveness in the diseased tissue and reduce general toxicity (Verdun *et al*., 1986).