UNIVERSITI PUTRA MALAYSIA

ENCAPSULATION OF TAMOXIFEN AND MAGNETIC NANOPARTICLES IN POLY LACTIC ACID USING SUPERCRITICAL ANTISOLVENT PROCESS

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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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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

ENCAPSULATION OF TAMOXIFEN AND MAGNETIC NANOPARTICLES IN POLY LACTIC ACID USING SUPERCRITICAL ANTISOLVENT PROCESS

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June 2020

Chairman : Prof Robiah binti Yunus, PhD
Faculty : Institute of Advanced Technology

Drug encapsulation offers advantages in controlled drug release and targeted drug delivery applications. Limited work had been carried out to encapsulate drug, magnetic nanoparticles and polymer in a single step process. The supercritical antisolvent (SAS) process offers a single step precipitation process and operates at a low temperature. Therefore, the SAS process has potential to encapsulate drug, polymer and magnetic nanoparticles. This study aims to use the SAS process to encapsulate tamoxifen (TAM) within a biodegradable polymer, Poly-L-Lactic acid (PLLA) for controlled drug delivery applications and later incorporated magnetic nanoparticles for targeted drug delivery applications.

The investigation began with manipulating operating pressure, the concentration of polymer, solution flow rate, and temperature of the system of the SAS system. The operating conditions affect the particle size and morphology of the encapsulated particles. The particle size of TAM-PLLA particles was successfully reduced from 1.85±0.06 µm to 0.43±0.03 µm with low particles agglomeration. The target particle size is below 1 µm to cater to the need to cross the tumor vasculature and to provide a stable colloidal system, which was covered in the later part of this study. TAM-PLLA particles have shown controlled release behavior by diffusion mechanism.

In the second stage of this study, the potential of the SAS process in developing drug-magnetic nanoparticles particles in polymer for targeted drug delivery was assessed. Tamoxifen was encapsulated with oleic acid magnetic nanoparticles (OAMNP) in poly-l-lactic acid. Introducing OAMNP in the formulation increases the complexity of the SAS process, as the quinary system is involved; rather than a typical quaternary system. This work has identified the method to incorporate OAMNP in sample preparation to ensure the success of the SAS process and

maintaining the magnetization characteristics of OAMNP in the final product. Polymer and OAMNP concentrations were manipulated to obtain the smallest particle size with non-agglomerated morphology and acceptable saturation magnetization value. Under the optimum encapsulation conditions, 43% of drug loading with a size of 0.67±0.09 μm and non-agglomerated particles. The superparamagnetic behaviour of formed particles with a saturation magnetization value of 4.1337 emu/g is achieved. These results are encouraging for tamoxifen controlled and targeted delivery applications.

The stability of particles in the biological environment was assessed in the colloidal stability study. Encapsulated particles were dispersed in various biological media such as Phosphate Buffered Solution (PBS), culture media, and culture media with serum. Factors such as concentration, time, and temperature were varied, and samples were evaluated based on particle size and zeta potential value. The condition that gives the most stable colloidal stability was identified.

Our final interest is to study the cytotoxicity of the final products in comparison to raw material. Brine shrimp assay was proposed as a mechanism to evaluate the cytotoxicity of TAM-OAMNP-PLLA. Lethal concentration LC50 was the concentration required to kill 50% of the sample population and has been used as a guideline to determine the toxicity of a sample. It was found that encapsulated tamoxifen (with and without) magnetic nanoparticles was non-toxic compared to raw tamoxifen, which possessed LC50 of 0.38 mg/mL as compared to 1.51 mg/mL (tamoxifen with PLLA) and 1.09 mg/mL (tamoxifen, magnetic nanoparticles with PLLA).

Overall, the SAS process has successfully produced encapsulated tamoxifen in Poly-l-lactic acid and tamoxifen with magnetic nanoparticles in Poly-l-lactic acid with particle size less than 1 μm and spherical morphology. The final products from the SAS process have proven to have potential in controlled and targeted drug delivery applications.

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

PENGKAPSULAN TAMOXIFEN DAN PARTIKEL NANO MAGNET DI DALAM ASID POLI LAKTIK MENGGUNAKAN KAEDAH GENTING ANTI PELARUT

Oleh

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Kaedah genting anti-pelarut (SAS) menggunakan bendalir superkritikal (SCF) untuk menghasilkan kapsulasi ubat di dalam polimer. Enkapsulasi ubat mempunyai kelebihan di dalam aplikasi penghantaran ubat terkawal dan tepat. Namun, terdapat limitasi dalam kajian untuk menghasilkan enkapsulasi ubat, polimer dan partikel nano magnet menggunakan satu proses. Proses SAS menawarkan satu langkah pemendakan dan beroperasi di suhu rendah, yang menjadikan proses ini amat sesuai untuk memproses bahan farmaseutikal. Oleh itu, proses SAS berpotensi untuk digunakan sebagai teknik pengkapsulan ubat, polimer dan partikel nano magent. Pengajian ini mensasarkan untuk menggunakan proses SAS untuk mensintesis tamoxifen yang dikapsulkan di dalam asid (L-poli laktik) dan kemudiannya menggabungkan partikel nano magnet di dalam formulasi.

Pengajian ini bermula dengan memanipulasi tekanan operasi, kepekatan polimer, kadar aliran larutan dan suhu sistem proses SAS. Keadaan operasi akan memberi kesan kepada saiz partikel dan keadaan morfologi ubat terkapsul. Saiz partikel yang terkandung telah berjaya dikurangkan dari 1.847 ± 0.06μm kepada 0.425 ± 0.03μm dengan pengurangan aglomerasi partikel. Saiz partikel ditetapkan kepada kurang dari 1 μm untuk memenuhi kriteria penghantaran untuk melepas pembuluh darah tumor di samping menyediakan sistem koloid yang stabil. Partikel TAM-PLLA telah menunjukkan profil penghantaran ubat terkawal melalui mekanisma penyebaran.

Di dalam bahagian kedua pengajian, potensi proses SAS di dalam menyediakan ubat dan partikel nano magnet di dalam polumer untuk penghantaran ubat secara tepat telah dikaji. Tamoxifen telah dienkapsulasi bersama partikel nano magnet disaluti asid oliek (OAMNP) di dalam asid (L-poli laktik). Kemasukan

OAMNP di dalam formulasi telah menabahkan kerumitan di dalam proses SAS kerana telah melibatkan proses berasaskan lima komponen, berbanding sistem berasaskan kuarter yang sering dijalankan menggunakan proses SAS. Pengajian ini telah mengenal pasti metod untuk memperkenalkan OAMNP di dalam penyediaan sample untuk memastikan kejayaan proses SAS dan bagi mengekalkan keupayaan magnetik OAMNP di dalam produk akhir. Kepekatan polimer dan OAMNP telah dimanipulasi untuk mendapatkan saiz partikel terkecil, tidak beraglomerasi dan nilai magnetisasi tepu yang sesuai. Di bawah proses enkapsulasi yang optimum, 43% pemerangkapan ubat telah dicapai dengan saiz partikel 0.67±0.09 μm dan sifat tidak beraglomerasi. Keupayaan superparamagnetic partikel mempunyai nilai magnetisasi tepu sebanyak 4.1337 emu/g. Keputusan ini menunjukkan potensi partikel untuk digunakan di dalam aplikasi penghantaran ubat secara terkawal dan tepat.

Kestabilan sistem koloid mengandungi partikel yang terhasil dari proses telah dinilai dengan menyebarkan partikel di dalam pelbagai larutan, PBS , media kultur dan media kultur bersama serum. Faktor seperti kepekatan larutan, masa dan suhu telah dipelbagaikan dan sampel telah dinilai berdasarkan saiz partikel dan nilai potensi zeta. Keadaan proses yang memberikan koloid yang stabil telah dikenal pasti.

Tumpuan akhir kami ialah untuk menentukan sitotoksisiti partikel dan membandingkannya dengan bahan mentah. Ujian *brine shrimp* telah dijadikan mekanisma untuk menguji sitotoksisiti partikel TAM-OAMNP-PLLA yang terhasil. Nilai media dos letal (LC_{50}) ialah nilai ketepuan untuk membunuh 50% populasi sampel dan telah digunakan sebagai tanda aras untuk menentukan toksisiti sesuatu sample. Dari ujikaji, kami telah menentukan tamoxifen yang diliputi oleh PLLA adalah tidak toksik (nilai median dos letal tamoxifen di dalam PLLA ialah 1.51 mg/mL manakala nilai median dos letal tamoxifen dan OAMNP di dalam PLLA ialah 1.09 mg/mL) berbanding tamoxifen yang dibekalkan pengeluar (nilai median dos letal ialah 0.38 mg/mL). Kesimpulannya, proses SAS telah menghasilkan tamoxifen yang dikapsulkan bersama partikel nano magnetik di dalam polimer terbiodegradasi dengan saiz partikel yang kurang dari 1 μm dan mempunyai bentuk sfera. Produk akhir dari proses SAS telah dibuktikan mempunyai potensi untuk aplikasi penghantaran ubat secara terkawal dan tepat.

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

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LIST OF ABBREVIATIONS

A.salina	Artemia Salina
ASES	Aerosol Solvent Extraction System
CM	Culture Media
CMWS	Culture Media without Serum
EDX	Energy Dispersive X-ray Spectroscopy
FBS	Fetal Bovine Serum
Fe_3O_4	Iron Oxide
FTIR	Fourier Transform Infrared Spectroscopy
GAS	Gas Anti Solvent
MNP	Magnetic Nanoparticles
MW	Molecular Weight
MRI	Magnetic Resonance Imaging
OAMNP	Oleic Acid-Coated Magnetic Nanoparticle
PBS	Phosphate Buffered Solution
PCA	Precipitation with Compressed Anti Solvent
PGSS	Particles from Gas Saturated Solutions
PLLA	Poly (L-lactic acid)
PLGA	Poly-L-Lactide co-glycolide
RESS	Rapid Expansion Supercritical Solutions
SC	Solid cosolvent
$scCO_2$	Supercritical Carbon Dioxide
SCF	Supercritical Fluid
SEDS	Solutions Enhanced Dispersion by Supercritical Fluid
SEM	Scanning Electron Microscopy
SLP	Solid Lipid Particles

SPIONs	Superparamagnetic Iron Oxide Nanoparticles
TAM	Tamoxifen
TAM-PLLA	Encapsulated tamoxifen in PLLA
TAM-OAMNP-PLLA	Encapsulated tamoxifen and OAMNP in PLLA
TEM	Transmission Electron Microscopy
VSM	Vibrating Sample Magnetometer
W/O/W	Water-in-oil-in-water
XRD	X-Ray Dispersion

LIST OF NOTATIONS

ρ	Density
LC	Drug loading capacity
X_C	Level of crystallinity
LC_{50}	Lethal Concentration
v	Relative velocity
We	Weber number
σ	Interfacial tension
D	Diameter

CHAPTER 1

INTRODUCTION

1.1 Background

The motivation in drug research development is to produce drug formulation that can escalate comfort and convenience to patients and increase patient compliances. Consequently, in 1952, the research and development in drugs delivery has steered its focus on sustained and controlled drug delivery specifically on establishment of controlled released mechanism before further advancing in targeted drug delivery area in 1990 (Park, 2015).

In conventional drug delivery, the drug is released rapidly and without any constraints, causing its bioavailability to be reduced, and the drug concentration decreases at the targeted tissue or cells. Patients are experiencing the side effects of drugs due to the release of drugs at non-targeted cells and healthy cells and also require multiple drug administration, which affects patients' comfort and convenience. In controlled drug and targeted drug delivery, drugs can be targeted to be released on the specific location and released in the therapeutic range preventing overdosing.

Figure 1.1 shows a controlled released vs. conventional released profile.

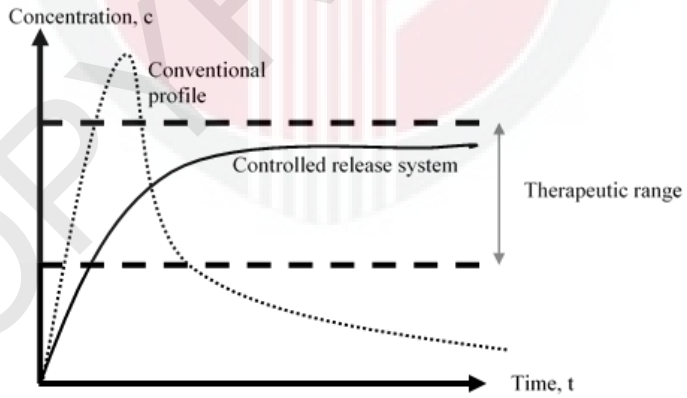

Figure 1.1: Controlled released system profile versus conventional released profile (Adapted from Kikic and Sist, 2000)

Numerous effort has been carried out by researchers to produce drugs with controlled and targeted drug delivery characteristics. In the nanotechnology area, efforts such as encapsulating drugs in nanoparticles (Cai et al., 2015), intercalating drugs in layered compounds (Rives et al., 2014), or attaching drugs

to tailored particle surfaces (Gonçalves et al., 2014) have been carried out. By encapsulating active ingredients in particulate carriers, a controlled drug release behaviour can be achieved as the drug will be released slowly from the coating materials by diffusion or erosion of the coating matrices. Conventional processes such as solvent evaporation, phase separation, spray-drying, and solvent diffusion are commonly used to synthesize encapsulated drugs. However, these methods have their limitation, such as extended operating hours (Pujara et al., 2017; Takeuchi et al., 2018). Conventional methods require multiple processes before recovering final product to reduce the possibility of solvent traces in the final product due to usage of a high volume of solvent in the process (Imbrogno et al., 2015; Pereira et al., 2016).

Limitations in the conventional encapsulation processes can be overcome by using multiple techniques offered by supercritical fluid (SCF) technology. SCF processes include Rapid Expansion Supercritical Solutions (RESS), Particles from Gas Saturated Solutions (PGSS), Gas Anti Solvent (GAS), Supercritical Anti Solvent (SAS) and Solution-Enhanced Dispersion by Supercritical Fluid (SEDS). Supercritical Carbon dioxide ($scCO_2$) is commonly used as supercritical fluid in these processes because carbon dioxide is inert, safe, easy to handle, easily available, has mild supercritical pressure and temperature point and non-toxic. In a supercritical fluid precipitation, $scCO_2$ can act as solvent, anti-solvent, co-solvent or solute, or propellant gas depending on the process requirements (Cocero et al., 2009; Kumar et al., 2014). The process that uses scCO2 as the solvent is known as RESS, where $scCO_2$ dissolves solutes before inducing precipitation by rapidly decreasing $scCO_2$ density, thus reducing the solubility of solutes in the $scCO_2$. Limitation in the RESS process is the limited choice of active ingredients that are soluble in $scCO_2$. This limitation can be overcome by using $scCO_2$ as an antisolvent in the process (SAS).

SAS process is one of the processes that use $scCO_2$ as antisolvent in the process. In the SAS process, solutes have to be miscible with the solvent but immiscible in $scCO_2$. In the meantime, the solvent should be miscible in $scCO_2$. Upon entering the precipitation vessel, which has been charged with $scCO_2$, $scCO_2$ will diffuse into solution droplets, dissolving the solvent, and creates a high supersaturation condition in the vessel that eventually leads to precipitation of the solutes.

Magnetic nanoparticles have been extensively studied to be applied in targeted drug delivery and targeted drug therapy (Chomoucka et al., 2010). In the targeted drug delivery application, drugs should be able to be transported to the centre of disease under various conditions without causing side effects to the body. Magnetic nanoparticles, which are generally derived from ferric oxide, are available at 10-20 nm in size (Lu et al., 2007).

Magnetic nanoparticles offer advantages that can be used in biomedical application due to many reasons, such as (Mornet et al., 2004; Lu et al., 2007):

1. Rapid response upon applied magnetic fields and negligible residual magnetism.
2. No risk of agglomeration at room temperature
3. Offers no harm to the human body except for patients with magnetized materials in the body
4. Can be used in hyperthermia treatment; a cancer therapy treatment using heat
5. Complimentary to a modern diagnostic method such as magnetic resonance imaging (MRI)
6. Ability to direct active ingredient directly to the vicinity of the targeted area in the body

The potential of co-precipitation of magnetic nanoparticles and active ingredient within particulate carriers offer more opportunities and possibilities in research and development on controlled drug delivery and drug targeting.

1.2 Problem Statement

Tamoxifen (TAM) is an anti-cancer drug that has been widely used in the treatment of breast cancer. However, patients who are consuming TAM for an extended time are experiencing side effects such as hot flushes, resulting in irregular menstrual cycle for premenopausal women, endometriosis, benign endometrial lesions, and increase risk of endometrial carcinoma amongst postmenopausal women (Mourits et al., 2001). Side effects of drugs are due to the interaction of drugs with healthy tissues in the body. A drug delivery system that can control the drug release rate and location of drug release is important to ensure the drug is released at a desirable dosage, within the therapeutic range and at the targeted location in the body. These characteristics may be achieved using the encapsulation of drugs within a suitable carrier.

Several methods have been employed to synthesized encapsulated drugs, such as emulsion solvent evaporation, spray drying, freeze-drying, emulsification, and melt granulation (Bohrey et al., 2016; Frank et al., 2018; Hamzehloo et al., 2017; Kaimainen et al., 2015; Mangwandi et al., 2015). However, these processes are limited due to multiple steps of process involved, an additional process to recover the final product in powder form, and problems with solvent traces in the final product.

The supercritical antisolvent process (SAS) has been chosen as the working process to encounter these abovementioned problems. The SAS process has advantages such as a simple, single-step precipitation process, the ability to recover the final product in powder form, and elimination of solvent in the final product. However, to avoid unsuccessful precipitation in the SAS process, special attention has to be given to the selection of solutes, solvent, and operating parameters. Unsuccessful precipitation in the SAS process is usually

due to partial solubility in CO_2 due to modification of the miscibility gap of solvent-antisolvent, which later will results in operating point falls in vapour/liquid region rather than supercritical region, unsuitable selection of encapsulating material and incomplete elimination of solvent which induced film formation of particles (Prosapio et al., 2018a).

In this work, tamoxifen is encapsulated within a biodegradable and biocompatible polymer, Poly-L-Lactic acid (PLLA) (English, 1998) for controlled drug delivery application. SAS process has been employed for PLLA micronization (Song et al., 2002) and as encapsulating material for drugs such as paclitaxel (Li et al., 2012), naproxen (Montes et al., 2014), astaxanthin (Liu et al., 2019), and 5-fluorouracil (Cuadra et al., 2020). To this date, no study has been carried out to encapsulate tamoxifen in PLLA using the SAS process yet. In the SAS process, process parameters such as operating pressure, temperature, polymer concentration, and solution flow rate gives effect on the physicochemical properties of the final product (Kalani and Yunus, 2011). To further understand the impact of each variable to the product's final characteristics, this work focuses on varying the process parameters and investigate its effects on the final product. There is a need to determine the process parameters of SAS that results in successful precipitation, gives a smaller particle, but less agglomeration particles since the final products from SAS are heavily influenced by SAS process parameters. Encapsulated tamoxifen is expected to have a controlled release behavior, which will be controlled by the swelling mechanism of the polymer. However, to ensure TAM-PLLA particles can be successfully delivered across the tumor vasculature has high retention time in the tumor site , particles has to possess size less than 600 nm (Chawla and Amiji, 2002). Thus, the final product from SAS process has to have minimum particle size for a better delivery and high retention time in the tumor site.

To explore the potential of tamoxifen in targeted drug delivery, tamoxifen has to be co-precipitated with magnetic nanoparticles (MNPs). In targeted drug delivery, a drug can be delivered directly to the vicinity of the target with the aid of an external magnet. The choice of MNPs in this work is oleic acid-coated magnetic nanoparticles (OAMNP). The selection of solvent is essential in the SAS process. The chosen solvent has to be able to dissolve all solutes (tamoxifen, PLLA, and OAMNP) and also has to be miscible with supercritical carbon dioxide. The other factor to be considered in the solvent selection is human innocuity, where the solvent has to be in class 3 (non-toxic) of pharmaceutical guidelines (Fages et al., 2004). However, to dissolve three solutes using one solvent is challenging. Dichloromethane (DCM) can be used to dissolve tamoxifen and PLLA (Ravikumara et al., 2016). However, OAMNP has not been able to dissolve in DCM. OAMNP has to be dispersed in a co-solvent that will help with the dispersion in DCM prior SAS process. A suitable co-solvent to disperse OAMNP with tamoxifen and PLLA in DCM has to be identified. The effect of operating parameters has to be studied to confirm a successful encapsulation of OAMNP with tamoxifen in PLLA. For potential applications in controlled and targeted drug delivery, the final product from the

SAS process has to display a controlled release profile and possess magnetic characteristics.

In the pharmaceutical research area, in-vivo tests and in-vitro tests are common tests that are conducted to study drug release behavior. However, a preliminary test prior in vivo test, which is known as the colloidal stability test is often overlooked. The colloidal stability test is important to be carried out before starting on any in vivo studies. Aggregations or clots formation of particles are most likely to happen after introducing the particles into a new, complex environment which are regulated by enzymes, salts, and pH (Lazzari et al., 2012). The colloidal stability test is a cheap, simple procedure but also a good indicator of the success of the in-vivo test. Colloidal stability results are important to determine the stability of optimized products from the SAS process in various biological environments which are simulated by varying types of biological fluid such as phosphate-buffered saline (PBS), culture medium with and without serum. Colloidal stability of a system can be observed from particle size, surface charges, and formation of agglomeration in the colloidal system.

According to Farré et al., (2009), the toxicity of a compound can be altered due to few factors such as particle size, shape, crystallinity, zeta potential, surface charges, and surface coating effect. A study conducted by Nazir et al., (2013) has concluded that brine shrimp lethality assay is an effective tool for pre-screening, designing, and synthesis of potent antitumor drugs. In-vivo cytotoxicity evaluation on tamoxifen against brine shrimp has been evaluated by Badisa et al., (2009). However no work on cytotoxic activity of encapsulated TAM-PLLA and TAM-OAMNP-PLLA using brine shrimp lethality assay has been carried out. The toxicity and detrimental effects of the final product from the SAS process are yet to be determined. Hence in this study, the safety evaluation of TAM-OAMNP-PLLA particles using brine shrimp lethality assay (BSLA) are to be conducted.

1.3 Contribution of the research

In this thesis, the usage of the Supercritical Anti Solvent Process to encapsulate tamoxifen in poly-l-lactic acid (PLLA) and encapsulation of tamoxifen and magnetic nanoparticles in PLLA are novel and has not been reported elsewhere. The SAS co-precipitation involving the formation of a quinary system, which are solvent, polymer, the active compound, magnetic nanoparticles (OAMNP), and supercritical carbon dioxide, has not been reported elsewhere too. The type of polymer, active ingredients, and operating parameters are unique for each system and vital for successful precipitation in the SAS process (Prosapio et al., 2018a). Identifying operating parameters that result in a successful precipitation process and understanding the effect of parameters on the physicochemical properties of formed particles in the SAS process will be useful for industries for scaling up purposes as well as researchers for good operational performance. This project will also identify the methodology to disperse OAMNP fully is the solvent of choice, which eventually will simplify the preparation process of materials prior SAS process. The understanding of the colloidal stability of

particles in a biological environment is critical to assess its fate after administration into the bloodstream. Brine shrimp lethality assay will provide useful information on the toxicity potential of the final product from the SAS process.

1.4 Objectives

The objectives of this study are:

i. To investigate the effects of Supercritical Anti Solvent (SAS) process parameters in encapsulating Tamoxifen in biodegradable polymer for controlled drug delivery.
ii. To evaluate the potential of using the Supercritical Anti Solvent (SAS) process in encapsulating tamoxifen and magnetic nanoparticles in biodegradable polymer for controlled and targeted drug delivery.
iii. To determine the colloidal stability of encapsulated tamoxifen and OAMNP in the polymer.
iv. To assess the toxicity of encapsulated tamoxifen and OAMNP in the polymer formed from the SAS process using brine shrimp lethality assay.

1.5 Thesis Outline

The thesis starts with Chapter 1, which comprises of problem statement and objectives of this work, followed by Chapter 2, which presents the literature review on properties of supercritical fluid and applications of supercritical fluid in the industry. Roles of supercritical fluid in the pharmaceutical industry and drug encapsulation methods and drug encapsulation using supercritical fluid are discussed. This chapter also includes a literature review on magnetic nanoparticles, conventional methods on attaching magnetic nanoparticles with drugs and polymer, and also characteristics of drug-magnetic nanoparticles-polymer composites. Literature review on colloidal stability, the interaction of forces involves in particle stabilization in a colloidal system, and efforts that have been taken to increase the stability of a colloidal system will also be covered in Chapter 2. This chapter also includes a literature review on toxicity study and various types of cytotoxicity tests.

In chapter 3, the materials and methods used in the study are clearly described. TAM used as starting material is unprocessed and used directly as per received from the supplier. Supercritical carbon dioxide is chosen as a working fluid due to attractive characteristics. Operating parameters in the encapsulation of TAM and polymer and also TAM-magnetic nanoparticles-polymer carried out using the SAS process are elucidated in this chapter. Characterization processes and procedures of formed particles are also explained in this chapter. Colloidal stability and cytotoxicity test of encapsulated TAM-PLLA and TAM-OAMNP-PLLA particles were explained in this chapter.
In chapter 4, the results for each of the objectives are presented. Chapter 4 is divided into four subchapters subjected to each of the objectives. In section 4.1, results and discussion for objective one are presented. A preliminary study to

determine the characteristics of encapsulated TAM compared with raw TAM and to determine whether the SAS process is a chemical process or mechanical process was conducted. The chapter continues with discussions on the effects of varying the operating parameters of the SAS process, starting with varying pressure, concentration, flow rate, and temperature. One factor at a time method has been chosen, and the optimum condition was selected at the smallest particle size and least agglomerated particles. The drug released behaviour of the optimized particles was observed and discussed. A drug release profile of TAM from polymer was established by fitting drug release data in several kinetic models. From the drug release data, a mathematical model that fits the drug release data was chosen. In section 4.2, oleic acid-coated magnetic nanoparticles (OAMNP) have been chosen to be encapsulated with TAM within polymer using the SAS process. A preliminary study to determine the magnetization value for encapsulated OAMNP in the polymer (without TAM) was carried out. In this study, the amount of polymer and OAMNP were varied, and the effect on particle size, morphology, and loading capacity were evaluated. The in-vivo drug release study was conducted, and drug release behaviour was proposed. A mathematical model that best fits with drug release behaviour was chosen. In section 4.3, a colloidal stability study was carried out for the optimized particles. A set of the colloidal system was prepared by dispersing encapsulated TAM in various medium; phosphate-buffered solution (PBS), complete media (CM) for cell culture, and culture media without serum (CMWS) at different condition. Variation of ultra-sonication condition, the temperature of colloid, and the concentration of medium was carried out. The formation of aggregates in various biological fluids and changes in particle size, the colour of medium, and the formation of sedimentation were monitored and observed. In section 4.4, results on the preliminary assessment of the toxicity of encapsulated drugs from the SAS process using brine shrimp analysis were presented. Toxicity after 24 and 48 hours of exposure was determined, and lethal concentration (LC50) value was determined.

Chapter 5 is a concluding chapter. All conclusions based on the objectives of the study are presented in this chapter, and recommendations for future work are proposed.

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