CONTROLLED-RELEASE OF CURCUMIN FROM POLY(LACTIDE-*CO*-GLYCOLIDE) ACID/ALBUMIN/CURCUMIN AND SILICA/ALBUMIN/CURCUMIN DRUG-DELIVERY SYSTEMS

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To my beloved:
Mohd. Azrin
Ameerul Hayqal
Sutinah
Pondi
Zainoriah
Zamri
and my siblings.

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ABSTRACT

In drug-delivery systems, the drug carriers should meet several prerequisites such as biocompatibility, biodegradability and lack of immune system activation, in order to play an effective role. In this study, a comprehensive attempt has been carried out to investigate the plausible intermolecular interactions of new drug-delivery systems, by correlating the drug release kinetic with the different types of carriers used. A hydrophilic metal oxide, silica (SiO_2), was used as the inorganic carrier, while poly(lactide-*co*-glycolide) (PLGA), a hydrophobic polyester, was used as the organic carrier. Based on these materials, the designed drug-delivery systems were SiO_2/albumin/curcumin (SiO_2/Alb/Cur) and PLGA/albumin/curcumin (PLGA/Alb/Cur), where albumin was used as the co-carrier, while curcumin as the hydrophobic model drug. The release of curcumin was proved to be controlled by the addition of albumin in the systems. It was expected that by using different kinds of carriers, different drug release patterns will be obtained, since the properties of the carriers can then influence the intermolecular interactions within the systems. Thus, the study of the intermolecular interaction of SiO_2/Alb/Cur systems was carried out by varying SiO_2 and albumin composition, and using different sources of SiO_2. Besides that, the study of the intermolecular interaction of PLGA/Alb/Cur was also done using different pretreatment methods and dispersion media of PLGA. The release experiments of albumin and curcumin were conducted via *in-vitro* procedures and phosphate buffer solution (pH 7) was used as the medium. The amounts of albumin and curcumin desorbed from the systems at different time intervals were monitored by UV-Visible spectroscopy (UV-Vis). The samples were characterized using diffuse reflectance UV-visible (DR-UV) spectroscopy, Fourier transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), specific surface area analysis and differential scanning calorimetry (DSC). The *in-vitro* studies show that the release of albumin and curcumin from SiO_2/Alb/Cur system is dependent on the compositions of SiO_2 and albumin, and the source of SiO_2 used (tetraethoxysilane (TEOS) and fumed silica). The release of albumin and curcumin was correlated with the intermolecular interaction between SiO_2, albumin, and curcumin. The addition of albumin as the co-carrier caused an increase in the total cumulative release amount of curcumin, suggesting that there was a competition between albumin and curcumin to interact with either SiO_2 or PLGA. Here, it was demonstrated that the amount of curcumin released was strongly affected by the carriers used. The use of SiO_2 as the carrier showed that release of curcumin followed pseudo-second order kinetics, while the use of PLGA showed a first-order kinetic at 49 h. It is concluded that a sustained and controlled drug release system can be achieved by using SiO_2 as the carrier. The different strategies and intermolecular interactions described here may be useful in designing a sustainable and controlled drug release system that can meet the medical demands of pharmaceutical applications.

ABSTRAK

Dalam sistem penghantaran dadah, sesuatu pembawa dadah mesti memenuhi beberapa prasyarat seperti biodegradasi, bioserasi dan mempunyai kadar pengaktifan sistem imun yang rendah, bagi membolehkannnya memainkan peranan yang efektif. Dalam kajian ini, satu percubaan komprehensif telah dijalankan untuk mengkaji interaksi antara molekul yang berkemungkinan dalam sistem penghantaran dadah baru, dengan menghubungkaitkan kinetik pelepasan dadah dengan pelbagai jenis pembawa. Oksida logam hidrofilik, silika, digunakan sebagai pembawa tak organik, manakala poliester hidrofobik, poli(laktida-*ko*-glikolida) (PLGA) digunakan sebagai pembawa organik. Berdasarkan bahan ini, sistem penghantaran dadah yang dibentuk adalah silika/albumin/kurkumin dan PLGA/albumin/kurkumin, dengan albumin digunakan sebagai ko-pembawa, manakala kurkumin sebagai model dadah hidrofobik. Pelepasan kurkumin telah dibuktikan dapat dikawal dengan penambahan albumin kepada sistem. Adalah dijangkakan dengan menggunakan pembawa yang berlainan, pola pelepasan dadah yang berlainan akan diperoleh kerana sifat pembawa boleh mempengaruhi interaksi antara molekul dalam sistem. Oleh itu, kajian interaksi antara molekul untuk sistem SiO_2/Alb/Cur telah dijalankan dengan pelbagai komposisi SiO_2 dan albumin, dan sumber SiO_2 yang berlainan. Selain itu, kajian interaksi antara molekul dalam sistem PLGA/Alb/Cur telah dilakukan dengan menggunakan kaedah prarawatan dan medium penyebaran PLGA yang berbeza. Eksperimen pelepasan albumin dan kurkumin telah dijalankan melalui prosedur *in vitro* dan larutan penimbal fosfat (pH 7) digunakan sebagai medium. Jumlah albumin dan kurkumin yang ternyahjerap daripada sistem dipantau pada selang masa berbeza menggunakan spektroskopi ultralembayung-nampak. Sampel telah dicirikan menggunakan spektroskopi ultralembayung-nampak pantulan terbaur, spektroskopi inframerah transformasi Fourier, analisis termogravimetri, mikroskop imbasan elektron, analisis luas permukaan spesifik dan kalorimetri pembezaan pengimbasan. Kajian *in-vitro* menunjukkan pelepasan albumin dan kurkumin daripada sistem SiO_2/Alb/Cur bergantung kepada komposisi SiO_2 dan albumin, dan sumber SiO_2 yang digunakan (tetraetoksisilana dan wasap silika). Pelepasan albumin dan kurkumin kemudiannya dikorelasikan dengan interaksi molekul antara SiO_2, albumin, dan kurkumin. Penambahan albumin sebagai ko-pembawa menyebabkan peningkatan jumlah pelepasan kumulatif untuk kurkumin, yang mencadangkan persaingan antara albumin dan kurkumin berinteraksi dengan SiO_2 atau PLGA. Telah ditunjukkan bahawa jumlah pelepasan kurkumin amat dipengaruhi oleh pembawa. Penggunaan SiO_2 sebagai pembawa menunjukkan pelepasan kurkumin mengikut kinetik tertib pseudo-kedua, manakala penggunaan PLGA menunjukkan kinetik tertib pertama pada 49 jam. Kesimpulannya, sistem penghantaran dadah terkawal dan beransur dapat dicapai dengan menggunakan SiO_2 sebagai pembawa. Strategi berbeza dan interaksi molekul yang diterangkan berkemungkinan boleh digunakan dalam mereka bentuk sistem pelepasan dadah terkawal dan beransur yang memenuhi permintaan perubatan untuk kegunaan farmaseutikal.

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%	-	Percent
~	-	Approximately
a.u.	-	Arbitrary unit
AC	-	Acetone
Alb	-	Albumin
B.E.T	-	Brunneur, Emmet and Teller
BJH	-	Barret-Joyner-Halenda
cm^{-1}	-	Per centimeter
Cur	-	Curcumin
Da	-	Dalton
DDS	-	Drug-delivery system
DR-UV	-	Diffuse Reflectance-Ultraviolet Visible Spectroscopy
DSC	-	Differential Scanning Calorimetry
DTG	-	Differential Thermogravimetric
EA	-	Ethyl acetate
FTIR	-	Fourier Transform Infrared Spectroscopy
g	-	gram
h	-	hour
MMA	-	Methyl methacrylate
MSNs	-	Mesoporous silica nanoparticles
n	-	Diffusion exponent
$NaBH_4$	-	Sodium borohydride
NH_3	-	Ammonia
PBS	-	Phosphate buffer solution
PLGA	-	Poly(lactide-*co*-glycolide) acid
RES	-	Reticuloendothelial system
SEM	-	Scanning Electron Miscroscopy

SiO_2	-	Silicon dioxide/Silica
TEOS	-	Tetraethoxysilane
TGA	-	Thermogravimetric Analysis
TiO_2	-	Titanium dioxide/Titania
UV	-	Ultraviolet
UV-VIS	-	Ultraviolet-Visible
XRD	-	X-Ray Diffraction

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Over the past few decades, there has been a significant growth in the drug-delivery field due to the underlying principle that drug-delivery technology could carry both therapeutic and commercial values to the health care products (Ahmadi *et al*., 2014). Furthermore, it has also been reported that drug delivery is one of the fastest-growing areas of the pharmaceuticals market, with approximately 10% annual growth and with the value of US $82 billion for the US market (Bruinewoud *et al*., 2005). It has been generally acknowledged that conventional drug-delivery system (DDS) is composed of a delivery device or dosage forms like a simple carrier without a lot of added value. Among the examples of conventional dosage forms are tablets or suspensions for oral administration, and solution for parental administration by injection (Bruinewoud *et al*., 2005).

The evolvement in the drug-delivery area led to the exploration of new dosing routes, for instance, transdermal, vaginal, pulmonary and sublingual (Wilson *et al*., 2011). Subsequently, more new drugs appeared with higher sensitive dose which often have poorer stabilities in a biological environment which is reported to have appeared in the 1990s (Barbe *et al*., 2004). This issue gave a stronger push towards the development of more efficient encapsulation and controlled-release of drug administration system. Therefore, a sustained and controlled-release of a drug-delivery system was progressively studied.

In the pharmaceutical industry, controlled drug-delivery systems (CDDS) have been widely applied as a strategic procedure to extend the specific potential of a drug product that reaches the human body systems (Siepmann *et al*., 2012). This type of DDS is mainly designed by researchers with the aim to deliver drugs within the desired range in the body continuously over a long period of time. Prolongation of the drug efficacy during administration process can be established by increasing the stability and enhancing the drug bioavailability (Wilson *et al*., 2011 and Bruinewoud *et al*., 2005). As the result, the frequency of the dose administered can be decreased considerably. Besides that, one more advantage promoted by the sustained delivery formulation contrary to the conventional dosing is the ability to avoid side effects when the drug is administered repeatedly (Zharapova *et al*., 2012). The examples of conventional drug dosing and controlled drug delivery are illustrated in Figure 1.1.

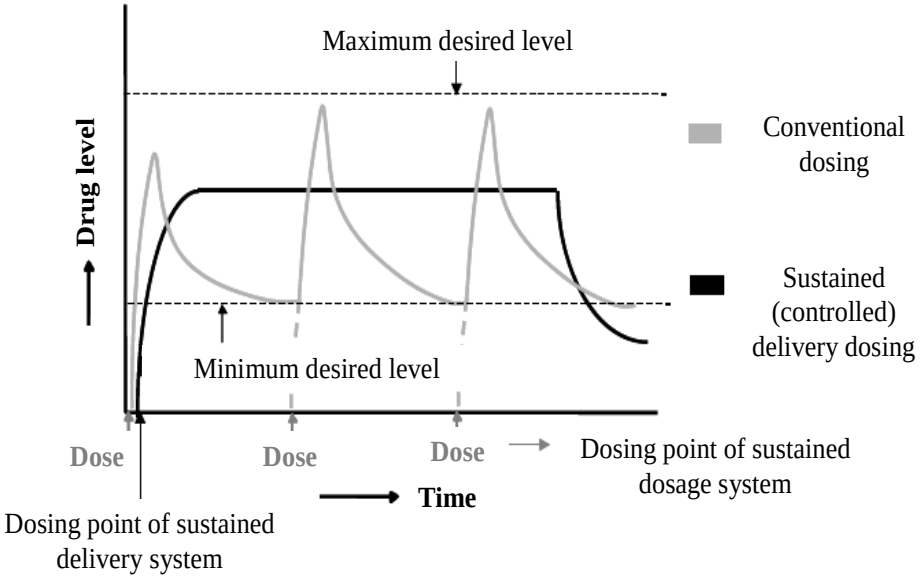

Figure 1.1: Conventional dosing versus sustained drug-delivery (Bruinewoud *et al*., 2005)

Therefore, it can be concluded that the foremost aim of a sustained and controlled-delivery system, is to design and control the drug releases at a specific rate over a defined period of time with minimal harm to the patient while improving human health (Bruinewoud *et al*., 2005 and Siepmann *et al*., 2012). Various aspects of a drug carrier need to be taken into account in order to play an effective role. The

carrier should satisfy several perquisites such an excellent biocompatibility, biodegradable to human system and lack of immune system activation (Wang, 2009, Ahmadi *et al*., 2014 and Horjacada *et al*., 2006).

On the other hand, numerous materials have been designed by the researchers to build up framework purposely for CDDS. Up until now, the drug-delivery system is designed according to the three kinds of carrier; inorganic, organic and inorganic-organic composite. Metal oxides such as silica (SiO_2) and titania (TiO_2) have been frequently employed as for inorganic-based drug-delivery system. In the case of the organic-based system, a wide range of biodegradable materials including natural and synthetic polymers have been utilized in the previous researches. Apart from that, the composite of inorganic and organic carriers is has also gained attention in the drug-delivery field. Table 1.1 summarizes the materials that have been used as drug carriers.

Table 1.1: Inorganic, organic and inorganic-organic drug carriers

Drug-delivery systems	**Drugs**	**Ref.**
Inorganic-carriers		
Calcium carbonate microcapsules	Lysozyme	Fujiwara *et al*., (2008)
Nanoporous TiO_2 matrices	Ibuprofen	Signoretto *et al*., (2011)
Mesoporous SiO_2 (SBA-15)	Ibuprofen	Ahmadi *et al*., (2014)
Mesoporous SiO_2 nanoparticles (MCM-41)	Ibuprofen and atenolol	Steven *et al*., (2014)
Organic-carriers		
Human Serum Albumin	Curcumin	Sahoo *et al*., (2008)
PLGA nanoparticles	Quercetin and catechin	Pool *et al*., (2012)
Hydroxypropylmethylcellulose (HPMC) matrix	Melatonin	Lee *et al*., (1999)
Polyvinyl acetate	Losartan potassium	Sarwar *et al*., (2012)

Continue on next page

Dendrimers	Artemether, camptothecin, cisplatin	Svenson *et al*., (2009)
Bovine Serum Albumin	Curcumin	Sadeghi *et al*., (2014)
Inorganic-organic composites		
Mesoporous SiO_2 (MCM)/apatite nanocomposite	Atenolol	Souza *et al*., (2008)
Chitosan coated mesoporous SiO_2 (MCM) nanoparticles	Ibuprofen	Popat *et al*., (2012)

Our study here focuses on the utilization of SiO_2 as an inorganic-based while Poly(lactide-*co*-glycolide) (PLGA) was employed as organic-based. SiO_2 is intrinsically hydrophilic metal oxide due to the presence of hydroxyl group on its surface (Horjacada *et al*., 2006). This natural hydrophilic character avoids elimination of SiO_2 by the reticuloendothelial system (RES). Specifically, RES is an immune system that works to evacuate any foreign entities from the body once it gets detected (Barbe *et al*., 2004). Therefore, tailoring SiO_2 as a carrier for the drug-delivery system can enhance circulation time of drug in blood stream. Amorphous SiO_2 is used in numerous applications such as in implant or coating relying on its biocompatibility aspect (Barbe *et al*., 2004). Besides that, it is a non-toxic material and has been used in food additives or vitamin supplements (Gangwar *et al*., 2013). Figure 1.2 illustrates SiO_2 particle decorated with hydroxyl surface.

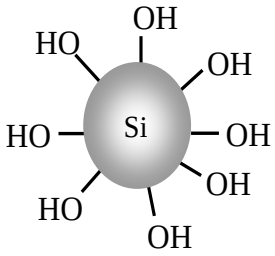

Figure 1.2: SiO_2 with hydroxyl surfaces

PLGA is relatively hydrophobic polyester which consists of hydroxyl-end group in the structure (Erbetta *et al*., 2012). It is built up by the subunit of lactic and glycolic acids, where these acids can be eliminated from the body as carbon dioxide and water through the tricarboxylic acid cycle (Cheng *et al*., 2008 and Gentile *et al*., 2014). One of the interesting aspects of PLGA is that the degree of hydrophobicity of PLGA can be tuned by varying the ratio of lactide to glycolide. The selection of the required ratio is important as this can strongly influence the physiochemical characteristics of the end-product and the dissolution of the drug. Figure 1.3 displays the chemical structure of PLGA and its monomer. Apart from that, the biodegradable character of PLGA is explained by the hydrolysis of its ester linkages in water (Makadia *et al*., 2011). PLGA is utilized in delivery system and bone tissue engineering applications because it is less toxic and biocompatible (Cheng *et al*., 2008 and Gentile *et al*., 2014). Incorporation of hydrophobic drug in PLGA particles increases circulation of material in blood stream. Various techniques have been employed to prepare PLGA nanoparticles such as emulsification-evaporation, emulsion-diffusion, salting-out, and precipitation (Song *et al*., 2006). Besides that, different types of solvent used in the dispersion of PLGA crystal, resulting in particular particle sizes of PLGA particle (Song *et al*., 2006).

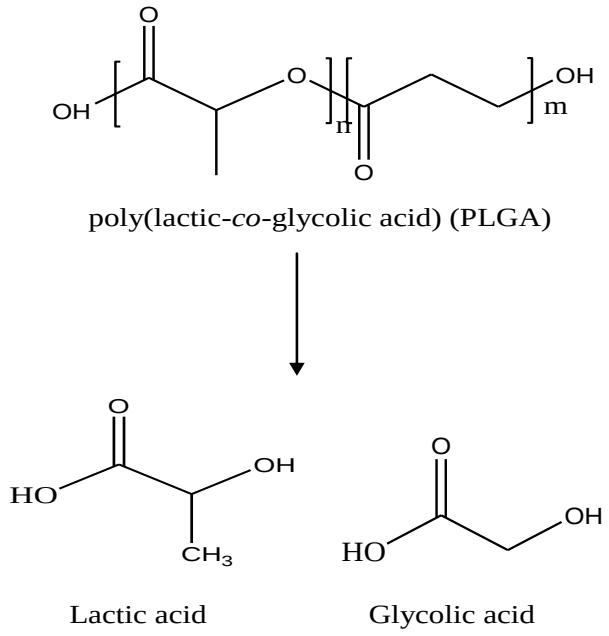

Figure 1.3: Chemical structure of PLGA and its monomers (Gentile *et al*., 2014)

In addition, we also intend to explore the functionality of albumin, the common component in a drug-delivery system, as co-carrier to control the release of the drug. It has been reported that the use of the protein as a drug-carrier does not affect the properties of the associated drug (Elzoghby *et al*., 2012 and Thomas *et al*., 2014). Here, egg white protein or ovalbumin is used as the source of albumin. Ovalbumin consists of 385 amino acid residues with a molecular weight of 47 kDa. It has an internal disulfide bond and four free sulphydryl groups (Elzoghby *et al*., 2012 and Huntington *et al*., 2001). Its tertiary structure was composed of nine α-helices and three β-sheets that folded into a compact globule supported mainly by the hydrogen bonds and disulfide bonds (Leunissen, 2001 and Bhattacharya *et al*., 2012). Albumin can enhance the apparent solubility of hydrophobic drug (Mohanta *et al*., 2013). Drugs could bind into the hydrophobic pocket of albumin via hydrophobic or van der Waals interactions. The presence of numerous functional groups in protein residues provides feasibility of drug-albumin interaction.

In this research, curcumin was used as the hydrophobic drug model. Curcumin, or diferuloylmethane, is a natural component of the rhizome of turmeric (*Curcuma longa*). Numerous studies on using curcumin as a therapeutic agent have been carried out due to its anti-oxidant, anti-inflammatory, anti-carcinogenic and anti-bacterial properties (Chereddy *et al*., 2013, Gangwar *et al*., 2013, Hatamie *et al*., 2012, Jithan *et al*., 2011 and Mathew *et al*., 2012). The anti-oxidant property of curcumin is contributed to the presence of phenolic –OH and *β*-diketone moiety that have the ability to scavenge the molecular species of active oxygen. Its hydrophobic nature and poor bioavailability leads to poor activity, low absorption, high rate of metabolism within the living system and rapid elimination from the body system. Curcumin undergoes rapid degradation in pH 7.4 buffer solution, where it is degraded more than 50% in 30 min release period (Leung *et al*., 2015). Therefore, there is a need for extensive research on this matter, which do not only improve the bioavailability of curcumin by increasing its solubility, but also to keep the multifunctional properties of the conjugated system. Figure 1.4 shows the chemical structure of curcumin with the presence of phenolic –OH and *β*-diketone moiety.

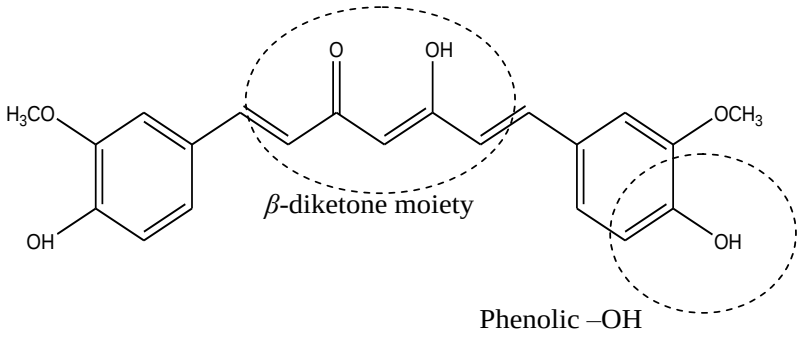

Figure 1.4: Chemical structure of curcumin (Leung *et al*., 2015)

The corresponding drug-delivery systems that were designed here are SiO_2/albumin/curcumin (SiO_2/Alb/Cur) and PLGA/albumin/curcumin (PLGA/Alb/Cur), where SiO_2 act as the inorganic carrier while PLGA is the organic carrier. It is interesting to note that the release trend of the drug can be affected by the type of carriers. In other words, the dissolution of the drug can be controlled depending on the carrier employed due to the particular intermolecular interaction within the system. Therefore, it can be summarized generally that the drug release from the system is correlated to the specific intermolecular interaction within the system and the type of carrier used. The presence of albumin as a co-carrier can provide in new role in term of intermolecular interaction in the drug-delivery system. It is realized that curcumin release can be controlled due to the existence of albumin in the system. Moreover, it has been demonstrated that conjugation of curcumin to albumin has increased its bioavailability characteristic (Thomas *et al*., 2014). Subsequently, the system designed here could be a promising drug-delivery system that related to the administration of hydrophobic pharmaceutical compound.

1.2 Statement of Problem

Generally, drug release is a process where a drug or any pharmaceutical compound is detached from its carrier, and then is associated to the absorption, distribution, metabolism and excretion (Singhvi *et al*., 2011). Significant efforts and advances in biotechnology have facilitated the production of new pharmaceutical

compounds. Hence, various drug-delivery systems or vehicles for the delivery of drug have been developed to satisfy the ever-growing demand for prolonged and better control of the drug administration. As a consequence, the controlled-released systems have been progressively conducted in the last few decades with the following objectives (Siepmann *et al*., 2012):

- to improve the appearance or enhance the circulation time of drug in the body
- to avoid elimination drug by RES system
- to improve the quality control in the production of drug products

In the past few years, there are numerous drug-delivery systems that have been designed in the administration of curcumin due to its favorable advantages in clinical aspects. Curcumin has been used as the remedy for some illness, for instance, inflammation and breast cancer. In conjunction with that, there are different formulations that have been studied such as PLGA loaded curcumin (Chereddy *et al*., 2013), albuminated curcumin (Thomas *et al*., 2014) and curcumin attached to the SiO_2 carrier (Gangwar *et al*., 2013).

However, these studies are more focused on the curcumin's solubility properties from the different formulation. To the best of our knowledge, a comprehensive study on controlled-released of curcumin from different kinds of carrier was less reported. Therefore, this study aims to design new drug-delivery systems that comprising both inorganic and organic material as the system-based with a co-carrier in the system. The novelty of the study can be related to the development of the new drug-delivery systems which are SiO_2/albumin/curcumin and PLGA/albumin/curcumin systems. Besides that, we also focused on the relationship between the drug release kinetic towards the particular intermolecular interactions exhibited by the drug-delivery systems with respects to SiO_2 and PLGA as system-based.

By using two different kinds of carriers, SiO_2 and PLGA in our case, it was expected that the drug release pattern could be different owing to the different characteristic of the carrier used. The hydrophilic character of SiO_2, due to its hydroxyl surface, can improve the solubility of curcumin and directly increase the

bioavailability in the clinical application. PLGA, on the other hand, is a hydrophobic polymer with the hydroxyl-end. Incorporation of curcumin within the PLGA matrix may prolong the circulation times in blood stream. The biocompability character of SiO_2 and the biodegradability property of PLGA towards the body system promote a safe and reliable drug-delivery system. It can be suggested that the properties of carrier may influence the release pattern of the drug, since the release mechanism between them is governed by its specific intermolecular interaction between the drug and the carrier. In a simple way, the property of the carrier itself affects the release mechanism of drug. In general, the interactions of a drug with carrier are associated through the hydrogen bond, hydrophilic and hydrophobic interactions, and Van der Waals force.

Figures 1.5 summarizes the schematic of the research approach and research questions in this study. In the inorganic-based system, SiO_2 particle was prepared using Stöber method prior to the addition of albumin and curcumin. The precursor of SiO_2 here was tetraethoxysilane (TEOS). The intermolecular interactions of the SiO_2/Alb/Cur systems were studied by varying the composition of SiO_2 and albumin, and using other type of SiO_2 which was fumed silica. For the preparation of PLGA-based systems, the intermolecular interaction of PLGA/Alb/Cur systems were explored by focusing on the different pre-treatment methods and different dispersion solvents of PLGA. The pre-treatment methods of PLGA were done by the addition of methyl methacrylate (MMA), and the addition of MMA followed by the irradiation under UV light. The pre-treatment procedures engaged here were purposely to modify the molecular structural of PLGA, which was theoretically, could promotes a good intermolecular interaction within the system. Moreover, the pre-treatment step proposed here reflects the novelty of PLGA that was used as a carrier for incorporation of drug. Most of the previous studies were using PLGA as the nanoparticles to encapsulate the associated drug (Akl *et al*., 2016, Dinda *et al*., 2011, Manoochehri *et al*., 2013 and Luz *et al*., 2012)

The engagement of albumin in the systems is expected to control the drug release. It has been reported that albumin may enhance the solubility of curcumin (Mohanta *et al*., 2013). Therefore, the utilization of albumin may increase the

bioavailability characteristic of curcumin which is beneficial in the clinical field. Besides that, it is also biocompatible material and widely abundance in nature (Li *et al*., 2009).

Preparation of SiO_2/Alb/Cur and PLGA/Alb/Cur systems present a new approach in developing a new controlled-release drug-delivery system. The crucial parts here were the comprehensive attempt to investigate the correlation between the drug releases from the designed drug-delivery systems towards its specific intermolecular interactions due to the different kind of carriers used. The release of curcumin together with albumin was explored in order to examine the effects of different parameters applied (SiO_2/Alb/Cur systems) and dissimilar preparation procedures and solvent used (PLGA/Alb/Cur systems). It is hypothesized that the release of curcumin and albumin from the carriers were strongly correlated with the intermolecular interactions within SiO_2/Alb/Cur and PLGA/Alb/Cur systems. Based on the above considerations, statement of the problem can be defined as follows: ***Release of curcumin can be controlled in the SiO_2- and PLGA-based systems with albumin as the co-carrier.***

This study proposed a new drug-delivery system involving controlled-release of drug in both inorganic and organic-based DDS. The impact of the engagement of albumin in the systems can influence the detachment of curcumin from SiO_2 and PLGA carrier. Besides that, the intermolecular interaction aspects on each system will be clarified in this study. This new design of DDS is expected to show pronounced advantages as a drug carrier in the administration of a hydrophobic compound (curcumin). A detailed exploration through this study will yield a fundamental understanding as well as the new intermolecular interaction between drug and carriers.

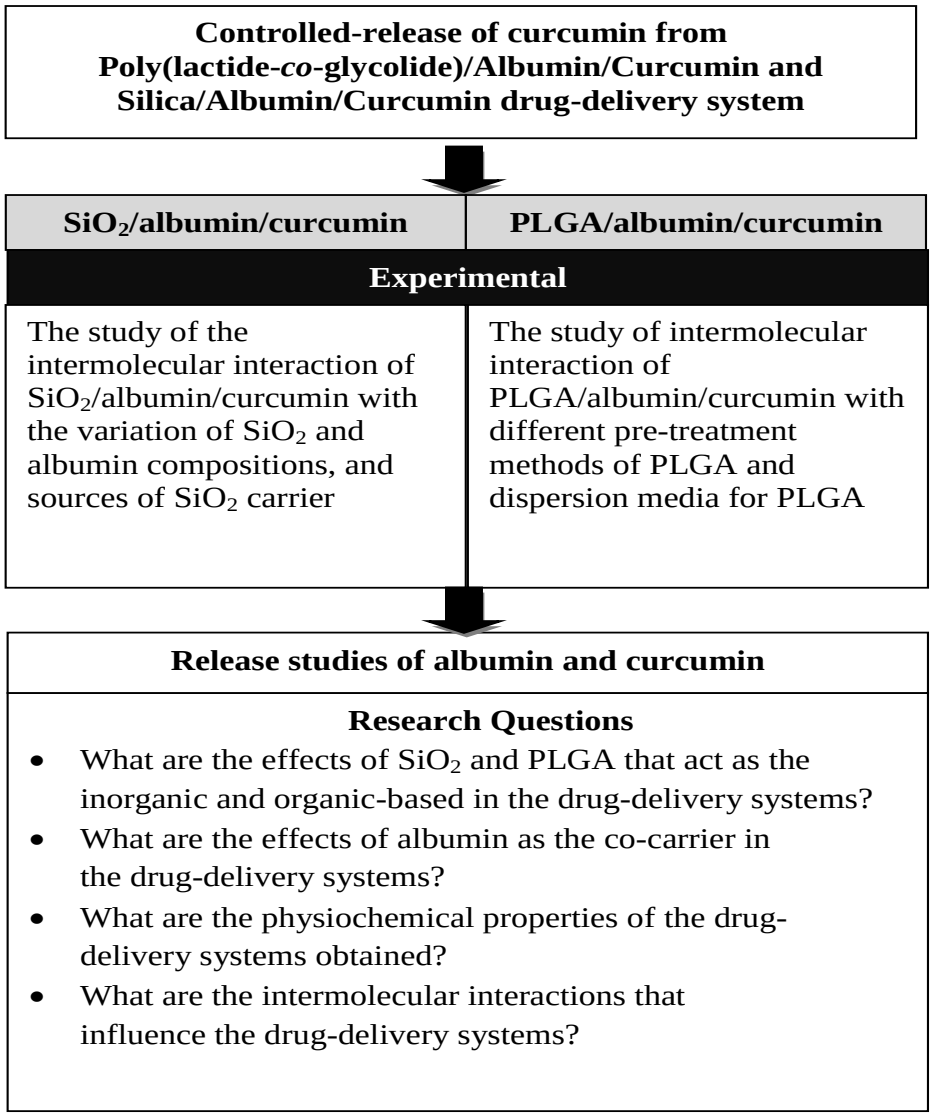

Figure 1.5: The schematic of the research approach and research questions

1.3 Objectives of Study

The ultimate goal of the present work is to design and prepare new drug-delivery systems that could achieve a controlled drug-delivery system (see Figure 1.1). The novelty of the work lies partly in the preparation of novel drug-delivery systems by using inorganic and organic materials as the system carrier. Besides that, the release kinetic of the albumin and curcumin are studied in order to elucidate the

mechanism of drug release. Therefore, this study has been carried out with the following objectives:

- To prepare and characterize inorganic and organic-based drug-delivery systems, SiO_2/Alb/Cur and PLGA/Alb/Cur.
- To evaluate the performance of the drug-delivery systems by carrying out release experiments of SiO_2/Alb/Cur and PLGA/Alb/Cur sytems.
- To investigate the intermolecular interaction between these two kinds of inorganic and organic carriers, which are SiO_2 and PLGA, with albumin as the co-carrier.

1.4 Thesis Outline

This thesis comprises of five chapters and the outlines of each chapter are as follows. **Chapter 1** contains an introduction of research background on the drug-delivery field followed by the research's problem statement. The objectives, scope and the significance of the present study are described in this chapter. **Chapter 2** comprises of literature reviews that are related to this study. **Chapter 3** discusses the experimental and characterization methods of both systems. **Chapter 4** contains the characterization outcomes, release performance results and kinetics study of the SiO_2/Alb/Cur system while **Chapter 5** contains the similar outlines for PLGA/Alb/Cur system including the comparative studies of both of the systems. **Chapter 6** discussed a concise conclusion based on the research findings and the recommendations for future study.

1.5 Scope of the Study

This study aims to develop a new drug-delivery system using SiO_2 and PLGA as the inorganic- and organic-based illustrated in the Figures 1.2 and 1.3. In the first system, the interaction between the albumin with the SiO_2 carrier was studied. Three

different SiO_2/albumin materials were prepared by dissimilar approaches; fumed silica/albumin (FS/Alb), fumed silica/albumin treated with $NaBH_4$ (FS/Alb-N) and SiO_2 sol from TEOS/Albumin (SS/Alb). Albumin release was carried out by the *in-vitro* method in phosphate buffer solution (PBS) at pH 7 and the amount of albumin desorbed from SiO_2 was detected by using UV-Visible (UV-Vis) spectrometer. Based on the characterization and cumulative release findings of SiO_2/albumin samples, the study was further carried out by using SiO_2 sol from TEOS as the SiO_2 precursor for all prepared SiO_2/Alb/Cur systems. There were three different parameters engaged in the SiO_2/Alb/Cur systems; different SiO_2/albumin composition, different albumin composition and the use of fumed silica as the SiO_2 source. Release of both albumin and curcumin were detected by UV-Vis. In order to determine the influence of albumin to the release of curcumin from SiO_2/Alb/Cur system, one sample consisting of SiO_2 and curcumin was prepared. The kinetic release orders are clarified accordingly. The obtained materials were characterized by diffuse reflectance UV-Visible (DR UV-Vis) spectrometer, Fourier transform infrared (FTIR) spectrometer, thermogravimetric analysis (TGA), Specific Surface Area (BET) Analysis, and scanning electron microscopy (SEM).

Apart from that, there were two approaches in the PLGA/Alb/Cur system. Firstly, this kind of system was prepared in two pre-treatment steps; PLGA added with methyl methacrylate and PLGA added with methyl methacrylate and followed by exposure to UV irradiation. Secondly, PLGA/Alb/Cur systems were prepared by using two different solvents for the dispersion of the PLGA polymer. The solvents were acetone and ethyl acetate. PLGA/Cur sample was prepared with the purpose to identify the impact of albumin present in the PLGA/Alb/Cur system. The obtained materials were also characterized by FTIR, DRUV, TGA, differential scanning calorimetry (DSC), BET and SEM. Release of both albumin and curcumin were detected by DRUV-Vis. Figure 1.6 summarizes concisely the scope of this research.

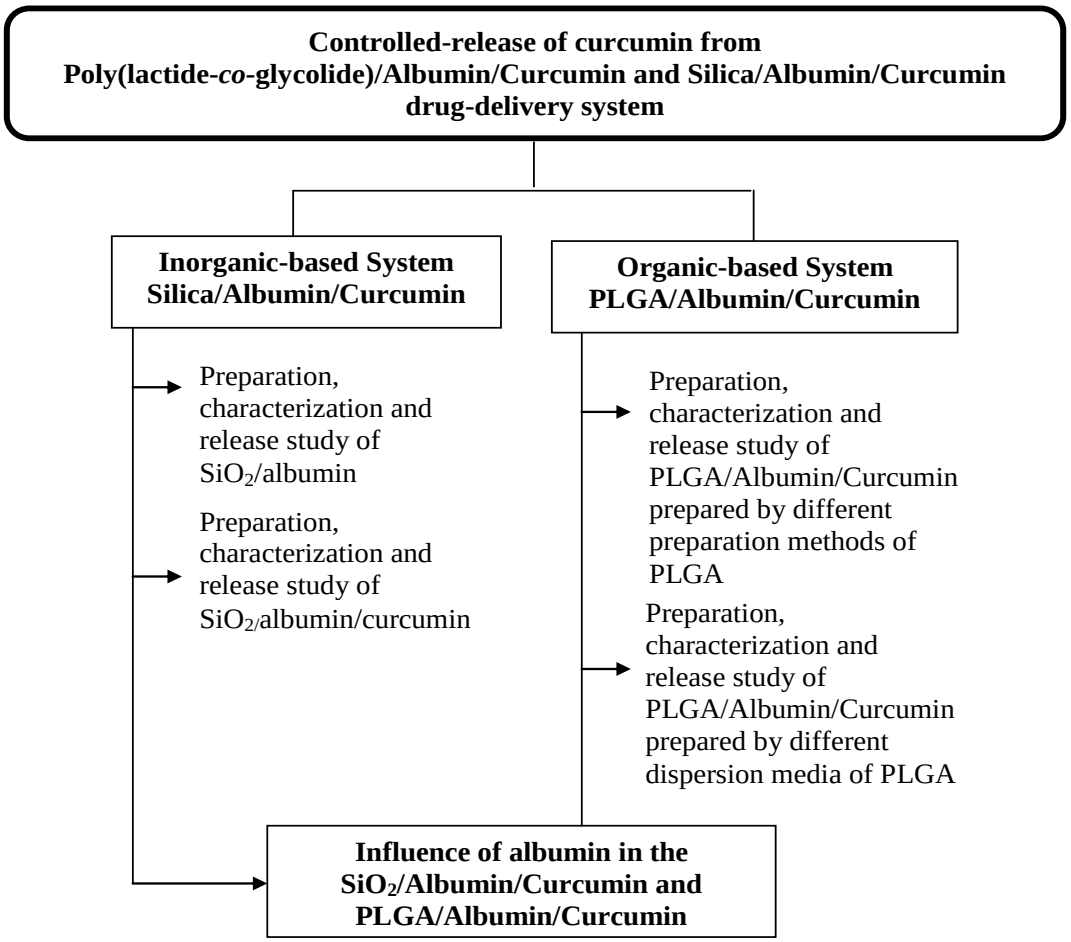

Figure 1.6: Diagram representation of scope of the study

1.6 Significance of the Study

This research comprehensively investigates the intermolecular interaction of new drug-delivery systems by correlating the drug release kinetics towards the different types of carriers. It would significantly contribute to the knowledge of controlled drug release and would be useful to the pharmaceutical industry in the future. Besides that, the new drug-delivery systems prepared here can be a potential system in the administration of other hydrophobic pharmaceutical compound in the future.

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