

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

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A thesis submitted in fulfilment of
requirements for the award of the degree of
Doctor of Philosophy (Chemistry)

Faculty of Science
Universiti Teknologi Malaysia

SEPTEMBER 2017

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

ACKNOWLEDGEMENT

Firstly, I would like to express my gratitude and thankfulness to my dearest supervisor, Prof. Dr. Hadi Nur for his continuous support of my Ph.D study and related research. His patience, keen motivation, scientific approach and immense knowledge really have helped me during my challenging journey. Without his guidance and support, this thesis cannot be completed to this extent.

Apart from that, I would like also to express my appreciation to Dr. Sheila Chandren, who always been there to assist me throughout my experimental and writing phase.

My sincere thanks also go to all the staffs of CSNANO Ibnu Sina Institute for their kind help and cooperation throughout my study period and who gave access to the laboratory and research facilities. I would also like to thanks my fellow labmates that are willingly to share their opinions and suggestions during my PhD studies.

Then, I would like also to thanks to my husband, parents, and my siblings for their support, encouragement and love throughout my PhD journey.

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 membolehkannya 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 SiO₂/Alb/Cur telah dijalankan dengan pelbagai komposisi SiO₂ dan albumin, dan sumber SiO₂ 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 terbaaur, 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 SiO₂/Alb/Cur bergantung kepada komposisi SiO₂ dan albumin, dan sumber SiO₂ yang digunakan (tetraetoksisilana dan wasap silika). Pelepasan albumin dan kurkumin kemudiannya dikorelasikan dengan interaksi molekul antara SiO₂, albumin, dan kurkumin. Penambahan albumin sebagai ko-pembawa menyebabkan peningkatan jumlah pelepasan kumulatif untuk kurkumin, yang mencadangkan persaingan antara albumin dan kurkumin berinteraksi dengan SiO₂ atau PLGA. Telah ditunjukkan bahawa jumlah pelepasan kurkumin amat dipengaruhi oleh pembawa. Penggunaan SiO₂ 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 SiO₂ 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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LIST OF ABBREVIATIONS

%	-	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- <i>co</i> -glycolide) acid
RES	-	Reticuloendothelial system
SEM	-	Scanning Electron Microscopy

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.

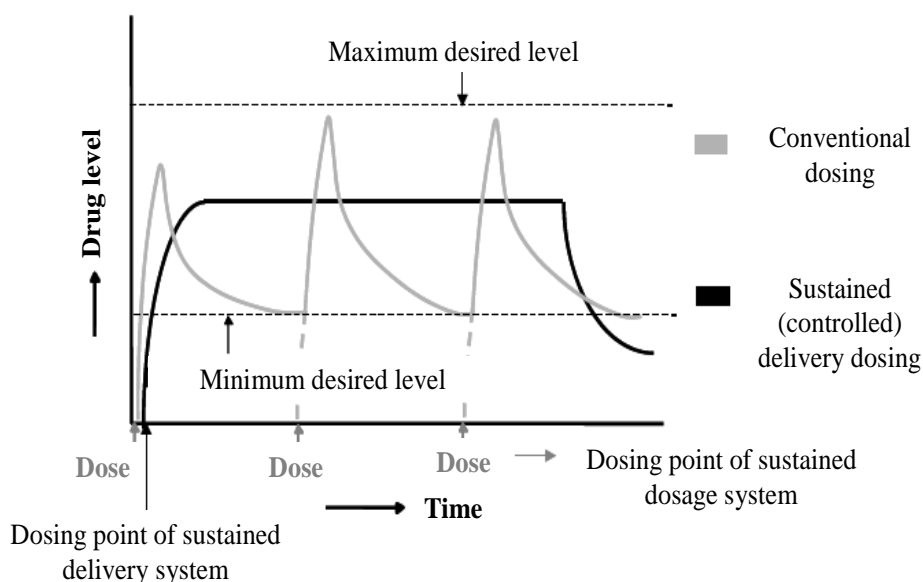


Figure 1.1: Conventional dosing versus sustained drug-delivery (Bruinewoud *et al.*, 2005)

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 prerequisites such as 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 (SiO₂) and titania (TiO₂) 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.
<u>Inorganic-carriers</u>		
Calcium carbonate microcapsules	Lysozyme	Fujiwara <i>et al.</i> , (2008)
Nanoporous TiO ₂ matrices	Ibuprofen	Signoretto <i>et al.</i> , (2011)
Mesoporous SiO ₂ (SBA-15)	Ibuprofen	Ahmadi <i>et al.</i> , (2014)
Mesoporous SiO ₂ nanoparticles (MCM-41)	Ibuprofen and atenolol	Steven <i>et al.</i> , (2014)
<u>Organic-carriers</u>		
Human Serum Albumin	Curcumin	Sahoo <i>et al.</i> , (2008)
PLGA nanoparticles	Quercetin and catechin	Pool <i>et al.</i> , (2012)
Hydroxypropylmethylcellulose (HPMC) matrix	Melatonin	Lee <i>et al.</i> , (1999)
Polyvinyl acetate	Losartan potassium	Sarwar <i>et al.</i> , (2012)

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Dendrimers	Artemether, camptothecin, cisplatin	Svenson <i>et al.</i> , (2009)
Bovine Serum Albumin	Curcumin	Sadeghi <i>et al.</i> , (2014)
<u>Inorganic-organic composites</u>		
Mesoporous SiO ₂ (MCM)/apatite nanocomposite	Atenolol	Souza <i>et al.</i> , (2008)
Chitosan coated mesoporous SiO ₂ (MCM) nanoparticles	Ibuprofen	Popat <i>et al.</i> , (2012)

Our study here focuses on the utilization of SiO₂ as an inorganic-based while Poly(lactide-*co*-glycolide) (PLGA) was employed as organic-based. SiO₂ 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 SiO₂ 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 SiO₂ as a carrier for the drug-delivery system can enhance circulation time of drug in blood stream. Amorphous SiO₂ 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 SiO₂ particle decorated with hydroxyl surface.

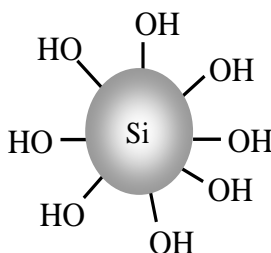


Figure 1.2: SiO₂ with hydroxyl surfaces

PLGA is relatively hydrophobic polyester which consists of hydroxyl-end group in the structure (Erбетта *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 physicochemical 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).

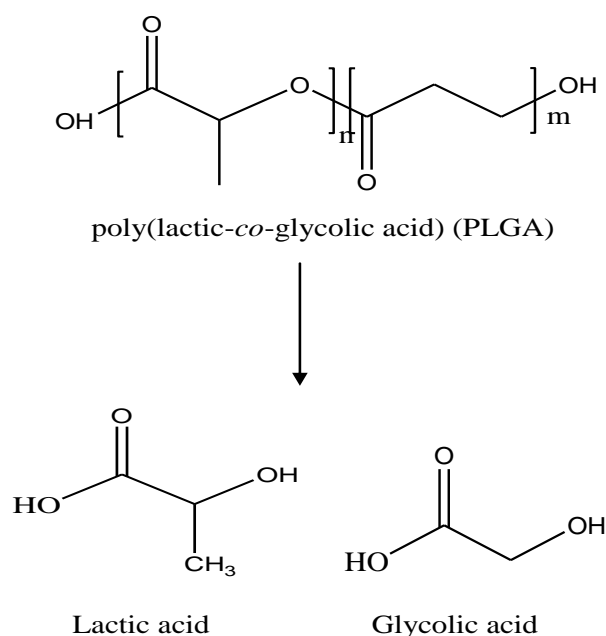


Figure 1.3: Chemical structure of PLGA and its monomers (Gentile *et al.*, 2014)

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 sulphhydryl 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 (Cherreddy *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 $-\text{OH}$ 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 $-\text{OH}$ and β -diketone moiety.

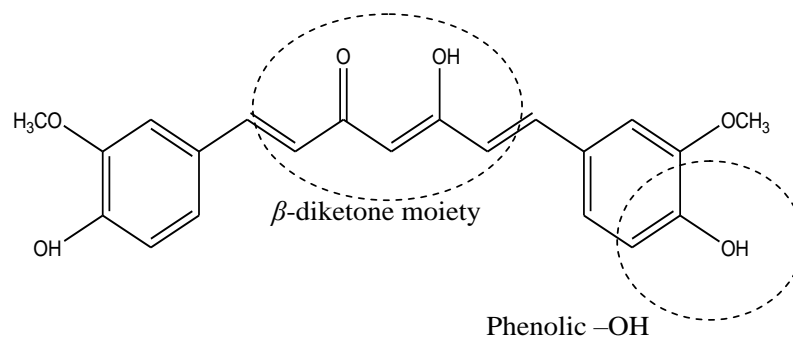


Figure 1.4: Chemical structure of curcumin (Leung *et al.*, 2015)

The corresponding drug-delivery systems that were designed here are SiO₂/albumin/curcumin (SiO₂/Alb/Cur) and PLGA/albumin/curcumin (PLGA/Alb/Cur), where SiO₂ 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 (Cherreddy *et al.*, 2013), albuminated curcumin (Thomas *et al.*, 2014) and curcumin attached to the SiO₂ 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 SiO₂/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 SiO₂ and PLGA as system-based.

By using two different kinds of carriers, SiO₂ 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 SiO₂, 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 biocompatibility character of SiO₂ 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.

Figure 1.5 summarizes the schematic of the research approach and research questions in this study. In the inorganic-based system, SiO₂ particle was prepared using Stöber method prior to the addition of albumin and curcumin. The precursor of SiO₂ here was tetraethoxysilane (TEOS). The intermolecular interactions of the SiO₂/Alb/Cur systems were studied by varying the composition of SiO₂ and albumin, and using other type of SiO₂ 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 promote 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 SiO₂/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 (SiO₂/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 SiO₂/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 SiO₂- 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 SiO₂ 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.

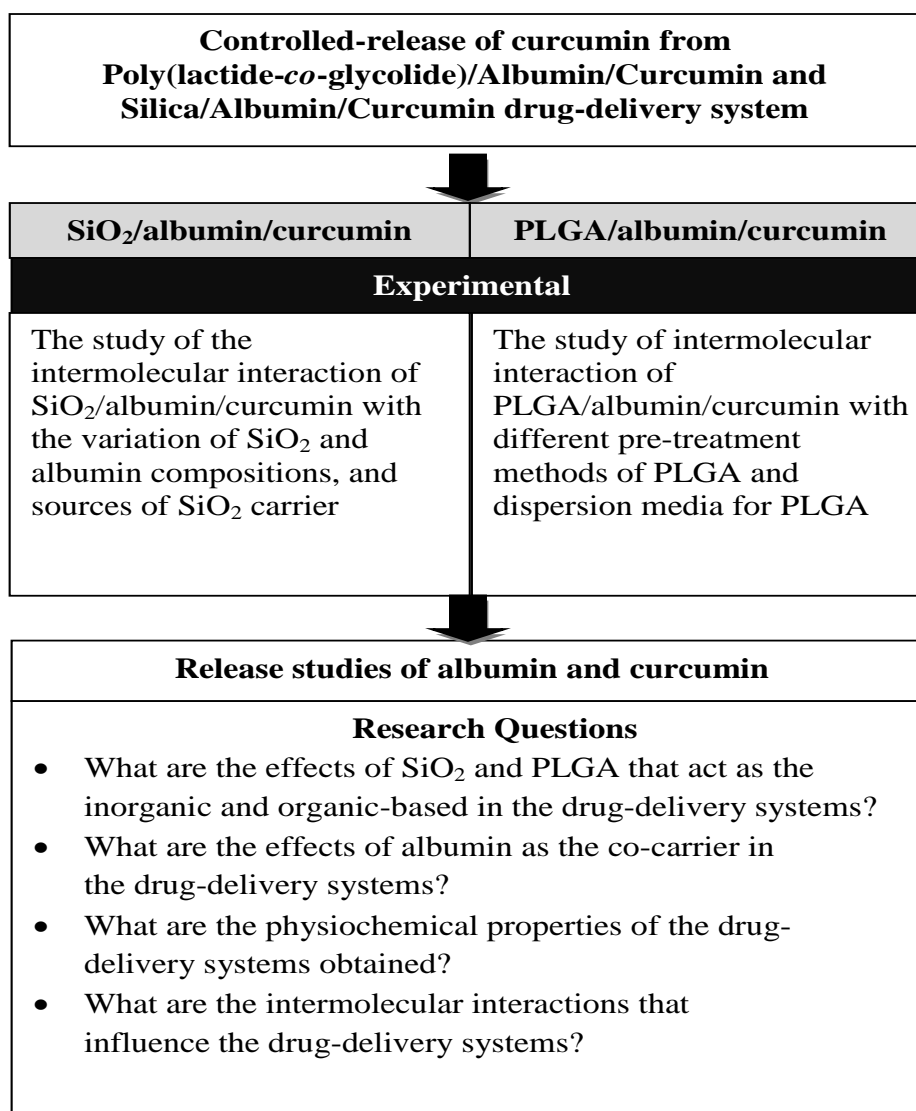


Figure 1.5: The schematic of the research approach and research questions

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, SiO₂/Alb/Cur and PLGA/Alb/Cur.
- To evaluate the performance of the drug-delivery systems by carrying out release experiments of SiO₂/Alb/Cur and PLGA/Alb/Cur systems.
- To investigate the intermolecular interaction between these two kinds of inorganic and organic carriers, which are SiO₂ 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 SiO₂/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 SiO₂ 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 SiO₂ carrier was studied. Three

different SiO₂/albumin materials were prepared by dissimilar approaches; fumed silica/albumin (FS/Alb), fumed silica/albumin treated with NaBH₄ (FS/Alb-N) and SiO₂ 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 SiO₂ was detected by using UV-Visible (UV-Vis) spectrometer. Based on the characterization and cumulative release findings of SiO₂/albumin samples, the study was further carried out by using SiO₂ sol from TEOS as the SiO₂ precursor for all prepared SiO₂/Alb/Cur systems. There were three different parameters engaged in the SiO₂/Alb/Cur systems; different SiO₂/albumin composition, different albumin composition and the use of fumed silica as the SiO₂ 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 SiO₂/Alb/Cur system, one sample consisting of SiO₂ 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.

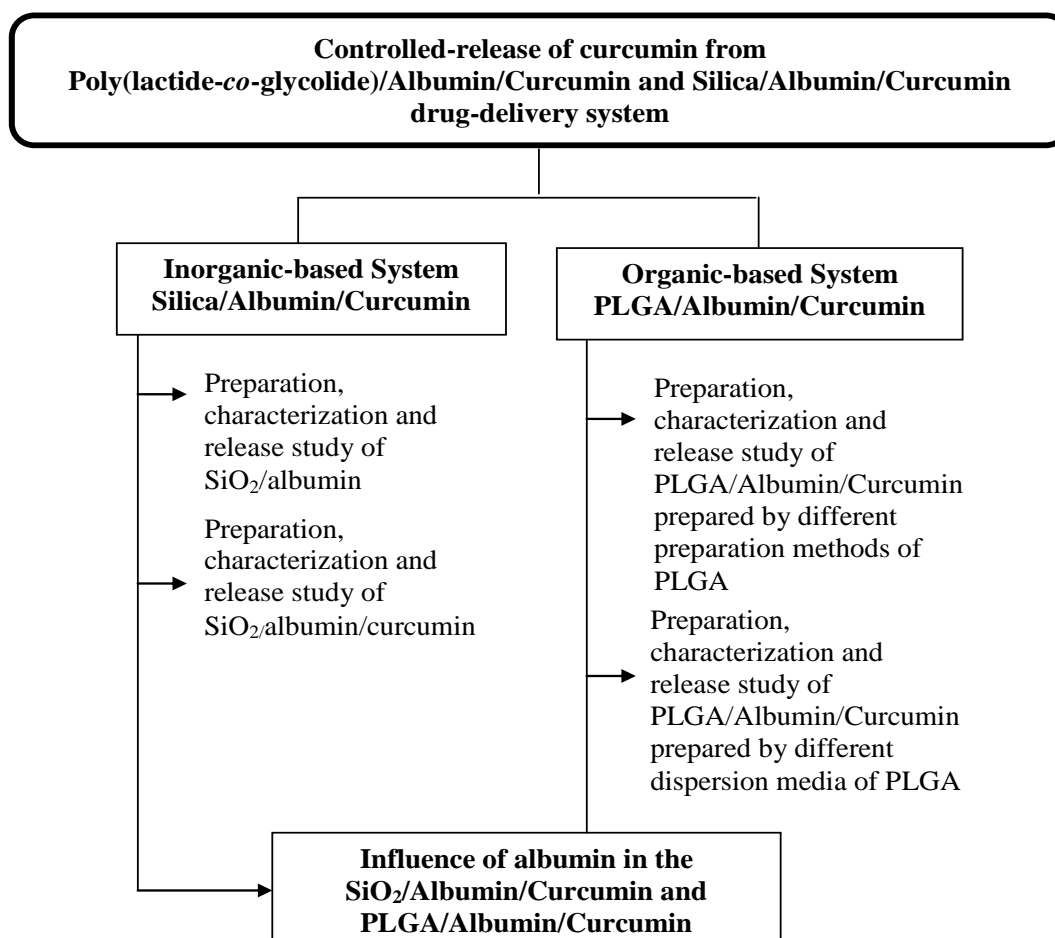


Figure 1.6: Diagram representation of scope of the study

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.

REFERENCES

- Ahmadi, E., Dehgannejad, N., Hashenikia, S., Ghasemnajad, M. and Tabebordbar, H. (2014). Synthesis and Surface Modification of Mesoporous Silica Nanoparticles and its Application as Carriers for Sustained Drug Delivery. *Drug Delivery*. 21(3), 164–172.
- Aiello, R., Giardano, G. and Testa, F. (2002). *Impact of Zeolites and Other Porous Materials on the New Technology at the Beginning of the New Millenium*. Amsterdam: Elsevier Science B. V. page 1134.
- Akl, M.A., Kartal-Hodzic, A., Oksanen, T., Ismael, H. R., Afouna, M. M., Yliperttula, M., Samy and A. M., Viitala, T. (2016). Factorial Design Formulation Optimization and *in vitro* Characterization of Curcumin-Loaded PLGA Nanoparticles for Colon Delivery. *Journal of Drug Delivery Science and Technology*. 32,10–20.
- Akram, M., Yu, H., Wang, L., Khalid, H., Abbasi, N. M., Abdin, Z., Chen, Y., Ren, F. and Saleem, M. (2016). Sustained Release of Hydrophilic Drug From Polyphosphazenes/Poly(Methyl Methacrylate) based Microspheres and Their Degradation Study. *Materials Science and Engineering C*. 58,169–179.
- Anand, P., Thomas, S.G., Kunnumakkara, A.B., Sundaram, C., Harikumara, K.B., Sung, B., Tharakan, S.T., Misra, K., Priyadarsini, I.K., Rajasekharan, K.N. and Aggarawal, B.B. (2008). Biological Activities of Curcumin and Its Analogues (Congeners) Made by Man and Mother Nature. *Biochemical Pharmacology*. 76,1590–1611.
- Arieh Ben-Naim (2012). *Hydrophobic Interactions*. Israel: Hebrew University of Jerusalem.
- Aswathy, R.G., Sivakumar, B., Brahatheewasaran, D., Fukuda, T., Yoshida, Y., Maekawa, T and Kumar, D.S. (2012). Biocompatible Fluorescent Zein Nanoparticles for Simultaneous Bioimaging and Drug Delivery Application. *Advances In Natural Sciences: Nanoscience And Nanotechnology*. 3,1–7.

- Barahuie, F., Hussein, M. Z., Gani, S. A., Fakurazi, S. and Zainal, Z. (2014). Anticancer Nanodelivery System with Controlled Release Property Based on Protocatechuate-Zinc Layered Hydroxide Nanohybrid. *International Journal of Nanomedicine*. 9, 3137–3149.
- Barbe, C., Barlett, J., Kong, L., Kim, F., Lin, H. Q. and Calleja, G. (2004). Silica Particles: A Novel Drug Delivery System. *Advance Matteredials*. 16, 1–18.
- Baroli, B., Shastri, V.P. and Langer, R. (2003). A Method to Protect Sensitive Molecules From a Light-induced Polymerizing Environment. *Journal of Pharmaceutical Science*. 92, 1186–1195.
- Bhattacharya, M., and Mukhopadhyay, S. (2012). Structural and Dynamical Insights into the Molten-Globule Form of Ovalbumin. *Journal of Physical Chemistry B*. 116, 520–531.
- Birnbaum, D.T., Kosmala, J.D., Henthorn, D.B. and Brannon-peppas, L. (2000). Controlled Release of β -Estradiol from PLGA Microparticles: The Effect of Organic Phase Solvent on Encapsulation and Release. *Journal of Controlled Release*. 65, 375–387.
- Bruinewoud, H. (2005). *Ultrasound-Induced Drug Release from Polymer Matrices : The Glass Transition Temperature as a Thermo-responsive Switch*. Eindhoven: Technische Universiteit Eindhoven.
- Charlessby, A. (1960). *Atomic Radiation and Polymers*. Oxford: Pergamon Press.
- Cheng, F.Y., Wang, P.H., Su, C.H., Tsai, T.L., Wu, P.C., Shieh, D.B., Chen, J.H. Hsieh, C.H. and Yeh, C.S. (2008). Stabilizer-free Poly(Lactide-co-Glycolide) Nanoparticles for Multimodal Biomedical Probes. *Biomaterials*. 29, 2104–2112.
- Cherreddy, K. K., Coco, R., Memvaga, P. B., Ucar, B., Rieux, A. Vandermeulen, G. and Pr at, V. (2013). Combined Effect of PLGA and Curcumin on Wound Healing Activity. *Journal of Controlled Release*. 171, 208–215.
- Chigwada, G., Kandare, E., Wang, D., Manoni, S., Mlambo, D., Wilkie, C.A. and Hossenlopp, M. (2008). Thermal Stability and Degradation Kinetics of Polystyrene/Organically-Modified Montmorillonite Nanocomposites. *Journal of Nanoscience and Nanotechnology*. 8, 1927–1936.
- Conrad, E. K., Nnaemeka, O. J. and Chris, A. O. (2015). Adsorptive Removal of Methylene Blue from Aqueous Solution Using Agricultural Waste:

- Equilibrium, Kinetic and Thermodynamic Studies. *American Journal of Chemistry and Materials Science*. 2(3), 14–25.
- Dinda, A., Biswal, I., Das, D., Si, S., Kumar, S., Barik, B.B. and Safhi, M.M. (2011). Effect of Stabilizers and Process Parameters for Budesonide Loaded PLGA-nanoparticles. *International Journal of Drug Delivery*. 3, 371–380.
- Elzoghby, A.O., Samy, W.M. and Elgindy, N.A. (2012). Protein-based Nanocarriers as Promising Drug and Gene Delivery Systems. *Journal of Controlled Release*. 161, 38–49.
- Erbetta, C. D. C., Alves, R. J., Resende, J. M., Freitas, R. F. S. and Sousa, R. G. (2012). Synthesis and Characterization of Poly(D,L-Lactide-co-Glycolide) Copolymer. *Journal of Biomaterials and Nanobiotechnology*. 3, 208-225.
- Erickson, H. P. (2009). Size and Shape of Protein Molecules at the Nanometer Level Determined by Sedimentation, Gel Filtration, and Electron Microscopy. *Biological Procedures Online*. 11(1), 32-51.
- Fenoglio, I., Fubini, B., Ghibaudi, E.M. and Turci, F. (2011). Multiple Aspects of the Interaction of Biomacromolecules with Inorganic Surfaces. *Advanced Drug Delivery Reviews*. 63,1186–1209.
- Fredenberg, S., Wahlgren, M., Reslow, M. and Axelson, A. (2011). The Mechanisms of Drug Release in Poly(Lactic-co-Glycolic Acid)-Based Drug Delivery Systems-A Review. *International Journal of Pharmaceutics*. 415, 34–52.
- Fu, K., Griebenow, Hsieh, L., Klibanov, A. M. and Langer, R. (1999). FTIR Characterization of the Secondary Structure of Proteins Encapsulated Within PLGA Microspheres. *Journal of Controlled Release*. 58, 357–366.
- Fujiwara, M., Shiokawa, K., Morigaki, K., Yingchun, Z. and Nakahara, Y. (2008). Calcium Carbonate Microcapsules Encapsulating Biomacromolecules. *Chemical Engineering Journal*. 137, 14–22.
- Furlan, P.Y., Scott, S.A. and Peaslee, M.H. (2010). FTIR-ATR Study Effects on Egg Albumin Secondary Structure. *Spectroscopy Letters*. 40, 475–482.
- Gangwar, R.K., Tomar, G.B., Dhumale, V.A., Zinjarde, S., Sharma, R. B. and Datar, S. (2013). Curcumin Conjugated Silica Nanoparticles for Improving Bioavailability and Its Anticancer Applications. *Journal of Agricultural and Food Chemistry*. 61, 9632–9637.

- Gap, X., Chan, W. C. W., and Nie, S. (2002). Quantum-Dot Nanocrystals for Ultrasensitive Biological Labeling and Multicolor Optical Encoding. *Journal of Biomedical Optics*. 7, 532–537.
- Gentile, P., Chion. V., Carmagnola, I. and Hatton, P.V. (2014). An Overview of Poly(lactic-co-glycolic) Acid (PLGA)-Based Biomaterials for Bone Tissue Engineering. *International Journal of Molecular Science*. 15, 3640–3659.
- Ghasemnejad, M., Ahmadi, E., Mohamadnia, Z., Doustgani, A. and Hashemikia, S. (2015). Functionalized Silica Nanoparticles as a Carrier for Betamethasone Sodium Phosphate: Drug Release Study and Statistical Optimization of Drug Loading by Response Surface Method. *Materials Science and Engineering C*. 56, 223–232.
- Hamam, F., and Al-Remawi, M. (2014). Novel Delivery System of Curcumin Through Transdermal Route using Sub-Micronized Particles Composed of Mesoporous Silica and Oleic Acid. *Journal of Functional Foods*. 8C, 87–99.
- Hatamie, S., Nouri, M., Karandikar, S.K., Kulkarni, A., Dhole, S.D., Phase, D.M. and Kale, S.N. (2012). Complexes of Cobalt Nanoparticles and Polyfunctional Curcumin as Antimicrobial Agents. *Materials Science and Engineering C*. 32, 92–97.
- Horcajada, P., Rámila, A., Boulahya, K., González-Calbet, J., and Vallet-Regi, M. (2004). Bioactivity in Ordered Mesoporous Materials. *Solid State Sciences*. 6(11), 1295–1300.
- Horcajada, Patricia., Serre, Christian., Vallet-Regi, Maria. and Gerard, Ferey. (2006). Metal-Organic Frameworks as Efficient Materials for Drug Delivery. *Angewandte Chemie*. 118, 6120–6124.
- Huang, X. and Brazel, C. S. (2001). On the Importance and Mechanisms of Burst Release in Matrix-Controlled Drug Delivery Systems. *Journal of Controlled Release*. 73, 121–136.
- Huntington, J.A. and Stein, P.E. (2001). Structure and Properties of Ovalbumin. *Journal of Chromatography B*. 756,189–198.
- Hussein, M. Z., Rahman, N. S. S. A., Sarijo, S. H. and Zainal, Z. (2012). Herbicide-Intercalated Zinc Layered Hydroxide Nanohybrid for a Dual-Guest Controlled Release Formulation. *International Journal of Molecular Sciences*. 13, 7328–7342.

- Ibrahim, I.A.M., Zikry, A.A.F. and A.Sharaf, M. (2010). Preparation of Spherical Silica Nanoparticles: Stober silica. *Journal of American Science*. 6, 985–989.
- Israelachvili, J.N. (2011). *Intermolecular and Surface Forces*. Amsterdam: Elsevier Science.
- Jahanshahi, M., and Babaei, Z. (2008). Protein Nanoparticle: A Unique System as Drug Delivery Vehicle. *African Journal of Biotechnology*. 7(25), 4929–4934.
- Jithan, AV., Madhavi, K., Madhavi, M. and Prabhakar, K. (2011). Preparation and Characterization of Albumin Nanoparticles Encapsulating Curcumin Intended for the Treatment of Breast Cancer. *International Journal of Pharmaceutical Investigation*. 1, 119–125.
- Joshi, J.R. and Patel, R.P. (2012). Role of Biodegradable Polymers in Drug Delivery. *International Journal of Current Pharmaceutical Response*. 4,74–81.
- Kang, M.H., Yong, W.C. and Park, K. (2003). PLGA–PEG Block Copolymers for Drug Formulation. *Drug Development and Delivery*. 3(5).
- Kaur, A., Jain, S. and Tiwaru, A. K. (2008). Mannan-Coated Gelatin Nanoparticles for Sustained and Targeted Delivery of Didanosine : *In Vitro* and *In Vivo* evaluation. *Acta Pharma*. 58(1), 61–74.
- Kaur, R. and Kaur, S. (2014). Role of Polymer in Drug Delivery. *Journal of Drug Delivery & Therapeutics*. 4, 32–36.
- Khabiri, M., Minofar, B., Brezovsky, J., Damborský, and Ettrich, R. (2013). Interaction of Organic Solvents with Protein Structures at Protein-Solvent Interface. *Journal of Molecular Modelling*. 19, 4701–4711.
- Korsmeyer, R. W., Gummy, R., Doelker, E., Buri, P. and Peppas, N. A. (1983). Mechanisms of Solute Release from Porous Hydrophilic Polymers. *International Journal of Pharmaceutics*. 15, 25–35.
- Kong, J. and Yu, S. (2007). Fourier Transform Infrared Spectroscopic Analysis of Protein Secondary Structures. *Acta Biochimica et Biophysica Sinica*. 39(8), 549–559.
- Kumar, K. V., Khaddour, I. A. and Gupta, V. K. (2010). A Pseudo Second-Order Kinetic Expression for Dissolution Kinetic Profiles of Solids in Solutions. *Industrial & Engineering Chemistry Research*. 49, 7257–7262.
- L'opez, T. Ortiz, E., Quintana, P., and Gonz'alez, R. D. (2007). A Nanostructured Titania Bioceramic Implantable Device Capable of Drug Delivery to the

- Temporal Lobe of The Brain. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*. 300, 3–10.
- Lai Sin Yuan (2013). *Preparation of Titanium(IV), Zinc(II), and Nickle(II) Complexes Silica-Based Catalysts for Limonene and 1-Octene Oxidation reactions*. Universiti Teknologi Malaysia: Tesis Doktor Falsafah.
- Langer, K., Balthasar, S., Vogel, V., Dinauer, N., Briesen, H., and Schubert, D. (2003). Optimization of the Preparation Process for Human Serum Albumin (HSA) Nanoparticles. *International Journal of Pharmacology*. 257, 169–180.
- Lee, B., Ryu, S., and Cui, J. (1999). Controlled Release of Dual Drug-Loaded Hydroxypropyl Methylcellulose Matrix Tablet using Drug-Containing Polymeric Coatings. *International Journal of Pharmaceutics*. 188, 71–80.
- Lee, T. Y., Roper, T. M., Jonsson, E. S., Kudyakov, I., Viswanathan, K., Nason, C., Guymon, C. A. and Hoyle, C. E. (2003). The Kinetics of Vinyl Acrylate Photopolymerization. *Polymer*. 44, 2859–2865.
- Leung, M., Harada, T., Dai, S. and Kee, T.W. (2015). Nanoprecipitation and Spectroscopic Characterization of Curcumin-Encapsulated Polyester Nanoparticles. *Langmuir*. 31, 11419–11427.
- Leunissen, M. (2001). An Essay on Several Aspects of Protein Crystallization Research. *Journal of Crystal Growth*. 2–36.
- Li, J. and Yao, P. (2009). Self-Assembly of Ibuprofen and Bovine Serum Albumin-Dextran Conjugates Leading to Effective Loading of the Drug. *Langmuir*. 25, 6385–6391.
- Liang, G., Shao, L., Wang, Y., Zhao, C., Chu, Y., Xiao, J., Zhao, Y, Li, X., and Yang, S. (2009). Exploration and Synthesis of Curcumin Analogues with Improved Structural Stability Both In Vitro And In Vivo as Cytotoxic Agents. *Bioorganic & Medicinal Chemistry*. 17, 2623–2631.
- Lowell, S., Shields, J. E., Thomas, M. A., and Thommes, M. (2004). *Characterization of Porous Solids and Powders: Surface Area, Pore Size and Density*. USA: Kluwer Academic.
- Lu, Y., Wang, Y., Goa, S., Wang, G., Yan, C., and Chen, D. (2009). Interaction of Quercetin with Ovalbumin: Spectroscopic and Molecular Modeling Studies. *Journal of Luminescence*. 129, 1048–1054.

- Luz, P. P., Magalhaes, L. G., Pereira, A. C., Cunha, W. R., Rodrigues, V., Marcio, L. and Silva, A. (2012). Curcumin-loaded into PLGA Nanoparticles. *Parasitology Research*. 110, 593–598.
- Maheshwari, R. K., Singh, A. K., Gaddipati, J., and Srimal, R. C. (2006). Multiple Biological Activities of Curcumin: A Short Review. *Life Sciences*. 78, 2081–2087.
- Makadia, H. K. and Siegel, S. J. (2011). Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. *Polymers*. 3, 1377–1397.
- Makowski, W., Mlekodaj, K., Gil, B., Roth, W. J., Marszalek, B., Kubu, M., Hudec, P., Smiešková, A. and Horňáček, M. (2014). Application of Quasi-Equilibrated Thermodesorption of Linear and Di-Branched Paraffin Molecules for Detailed Porosity Characterization of the Mono-Layered Zeolite MCM-56, in Comparison with MCM-22 And ZSM-5. *Dalton Transactions*. 43, 10574–10583.
- Manoochehri, S., Darvishi, B., Kamalini, G., Amini, M., Fallah, M., Ostad, S. N., Atyabi, F. and Dinarvand, R. (2013). Surface Modification of PLGA Nanoparticles via Human Serum Albumin Conjugation for Controlled Delivery of Docetaxel. *Journal of Pharmaceutical Sciences*. 21(58), 1–10.
- Mathew, A., Fukuda, T., Nagaoka, Y., Hasumura, T., Morimoto, H., Yoshida, Y., Maekawa, T., Venugopal, K. and Kumar, D. S. (2012). Curcumin Loaded PLGA Nanoparticles Conjugated with Tet-1 Peptide for Potential Use in Alzheimer's Disease. *PLOS ONE*. 7(3), 1–10.
- McCool, B., Murphy, L., and Tripp, C. P. (2006). A Simple FTIR Technique for Estimating the Surface Area of Silica Powders and Films. *Journal of Colloid and Interface Science*. 295, 294–298.
- Mohanta, V., Madras, G. and Patil, S. 2013. Albumin-Mediated Incorporation Of Water-Insoluble Therapeutics In Layer-By-Layer Assembled Thin Films And Microcapsules. *Journal of Material Chemistry*. 1, 4819–4827.
- Mufamadi, M. S., Maluta., Pillay, Viness., E.Choonara. and Valence, M.K.Ndesendo. (2011). A Review on Composite Liposomal Technologies for Specialized Drug Delivery. *Journal of Drug Delivery*. 1–19.
- Munin, A. and Edwards-Levy, F. (2011). Encapsulation of Natural Polyphenolic Compounds; a Review. *Pharmaceutics*. 3, 793–829.

- Nafisi, S., Sadeghi, G.B. and Panahy, A. (2011). Interaction of Aspirin and Vitamin C with Bovine Serum Albumin. *Journal of Photochemistry and Photobiology B: Biology*. 105, 198–202.
- Noyes, A. A. and Whitney, W. R. (1987). The Rate of Solution of Solid Substances in Their Own Solutions. *Journal of the American Chemical Society*, 19, 930–934.
- Orive, G., Hernandez, R.M., Gascon, A.R., Dominguez-Gily, A. and Pedraz, J. L. (2003). Drug Delivery in Biotechnology: Present and Future. *Current Opinion in Biotechnology*. 14, 659–664.
- Park, K. (2014). Controlled Drug Delivery Systems : Past Forward and Future Back. *Journal of Controlled Release*. 190, 3–8.
- Partwardhan, S.V., Patwardhan, G. and Perry, C. C. (2007). Interactions of Biomolecules with Inorganic Materials : Principles, Applications and Future Prospects. *Journal of Material Chemistry*. 17, 2875–2884.
- Patil, G.V. (2003). Biopolymer Albumin for Dianogsis and in Drug Delivery. *Drug Development Research*. 58, 219–247.
- Pauling, L., Corey, R.B., and Banson, H. R. (1951). The Structure of Proteins: Two Hydrogen-bonded Helical Configurations of the Polypeptide Chain. *Proceedings of the National Academy of Sciences of the United States of America*. 37, 205–211.
- Pavia, D. L., Lampman, G. M., Kriz, G. S., and Vyvyan, J. R. (2014). *Introduction to Spectroscopy*. United States of America : Cengage Learning. 5th Ed.
- Pillai, J. J., Kumar, A., Thulasidasan, T., Anto, R. J., Devika. N. C., Ashawanikumar, N. and Kumar, G. S. V. (2015). Curcumin Entrapped Folic Acid Conjugated PLGA-PEG Nanoparticles Exhibit Enhanced Anticancer Activity by Site Specific Delivery. *RSC Advances*. 5, 25518–25524.
- Poncin-Epaillard, F., Vrlinic, T., Debarnot, D., Mozetic, M., Coudreuse, A., Legeay, G., Moualij, B.E., and Zorzi, W. (2012). Surface Treatment of Polymeric Materials Controlling the Adhesion of Biomolecules. *Journal of Functional Biomaterials*. 3, 528–543.
- Pool, H., Quintanar, D., Figueroa, J.D.D., Mano, C.M., Bechara, J.E.H., Godinez, L.A. and Mendoza, S. (2012). Antioxidant Effects of Quercetin and Catechin Encapsulated into PLGA Nanoparticles. *Journal of Nanomaterials* . 1–12.

- Popat, A., Liu, J., Lua, G.Q. and Qiao, S.Z. (2012). A pH-Responsive Drug Delivery System Based on Chitosan Coated Mesoporous Silica Nanoparticles. *Journal of Material Chemistry*. 1–6.
- Preetha, P., Rao, A.S. and Pushpalata, P. (2015). Biphasic Drug Delivery in Controlled Release Formulations-A Review. *International Journal of Pharmacy & Technology*. 6, 3046–3060.
- Reddy, A. C., Sudharshan, E. Rao, A. G. and Lokesh, B. R. (1999). Interaction of Curcumin with Human Serum Albumin-A Spectroscopic Study. *Lipids*. 34(10), 1025–1029.
- Sadeghi, R., Moosavi-Movahedi, A. A., Emam-jomeh, Z. Kalbaso, A. Razavi, S. H., Karimi, M. and Kokini, J.(2014). The Effect of Different Desolvating Agents on BSA Nanoparticle Properties and Encapsulation of Curcumin. *Journal of Nanoparticle Research*. 16, 1–14.
- Sah, H. (1997). Microencapsulation Techniques using Ethyl Acetate as A Dispersed Solvent: Effects of Its Extraction Rate on the Characteristics of PLGA Microspheres. *Journal of Controlled Release*. 47, 233–245.
- Sahoo, B. K., Ghosh, K. S. and Dasgupta, S. (2008). Molecular Interactions of Isoxazolcurcumin with Human Serum Albumin: Spectroscopic and Molecular Modeling Studies. *Biopolymers*. 91(2), 108–120.
- Santhi, K., Dhanaraj, S.A., Rajendran, S.D., Raja, K., Ponnusankar, S. and Suresh, B. (1999). Nonliposomal Approach- A Study of Preparation of Egg Albumin Nanospheres Containing Amphotericin-B. *Drug Development and Industrial Pharmacy*. 25, 547–551.
- Sarwar, M. S. And Hossain, M. S. (2012). Development and Evaluation of Sustained Release Losartan Potassium Matrix Tablet using Kollidon SR as Release Retardant. *Brazilian Journal of Pharmaceutical Sciences*. 48, 621–628.
- Sasaki, J. and Kichida, M. (2012). *Curcumin Biosynthesis, Medicinal Uses And Health Benefits*. New York : Nova Science Publishers.
- Scarano, W., Souza, P.D. and Stenzel, M.H. (2014). Dual-drug delivery of Curcumin and Platinum Drugs in Polymeric Micelles Enhances the Synergistic Effects: A Double Act for the Treatment of Multidrug-resistant Cancer. *Biomaterial Science*. 1–12.
- Schmid, F. (2001). *Biological Macromolecules: UV-Visible Spectrophotometry*. University of Bayreuth: Germany Macmillan Publishers Ltd. 1–4.

- Siepmann, J. and Siepmann, F. (2012). Modeling of Diffusion Controlled Drug Delivery. *Journal of Controlled Release*. 161, 351–362.
- Siepmann, J., A. Siegel, R. and Rathbone, M.J. 2012. *Fundamentals and Applications of Controlled Release Drug Delivery*. Advances in Delivery Science and Technology. Springer.
- Signoretto, M., Ghedini, E., Nichele, V., Pinna, F., Crocellà, V. and Cerrato, G. (2011). Effect of Textural Properties on the Drug Delivery Behaviour of Nanoporous TiO₂ Matrices. *Microporous and Mesoporous Materials*. 139, 189–196.
- Silva-Buzanello, R. A., Souza, M. T., Oliveira, A. A., Bona, E., Leimann, F. V., Filho, L. C., Araújo, H. H., Ferreira, S. R. S. and Gonçalves, O. H. (2016). Preparation of Curcumin-Loaded Nanoparticles and Determination of the Antioxidant Potential of Curcumin after Encapsulation. *Polímeros*, 26(3), 207–214.
- Sionkowska, A., Planecka, A., Lewandowska, K., Kaczmarek, B. and Szarszewska, P. (2013). Influence Of UV-Irradiation on Molecular Weight of Chitosan. *Progress on Chemistry and Application of Chitin and Its XVIII*, 21–28.
- Song, K.C., Lee, H.S., Choung, I.Y., Cho, K.I., Ahn, Y. and Choi, E.J. (2006). The Effect of Type of Organic Phase Solvents on the Particle Size of Poly(D,L-lactide-co-glycolide) Nanoparticles. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*. 276, 162–167.
- Sousa, Z., Souza, K. C., and Sousa, E. M. B. (2008). Mesoporous Silica/Apatite Nanocomposite: Special Synthesis Route to Control Local Drug Delivery. *Acta Biomaterialia*. 4, 671–679.
- Souza, M. C. and Marchetti, J. M. (2012). Development of Albendazole Sulfoxide-Loaded Eudragit Microparticles: A Potential Strategy to Improve the Drug Bioavailability. *Advanced Powder Technology*. 23, 801–807.
- Steven, C. R., Busby, G. A., Mather, C., Tariq, B., Briuglia, M. L., Lamprou, D. A., Urquhart, A. J., Grant, M.H. and Parthwardhan, S. H. (2014). Bioinspired Silica as Drug Delivery Systems and Their Biocompatibility. *Journal of Materials Chemistry B*. 2, 5028–5042.
- Stuart, B. (2004). *Infrared Spectroscopy: Fundamentals and Applications*. John Wiley & Sons.

- Svenson, S. (2009). Dendrimers as Versatile Platform in Drug Delivery Applications. *European Journal of Pharmaceutics and Biopharmaceutics*. 71,445–462.
- Tewes, F., Munnier, E., Antoon, L., Ngaboni Okassa, L., Cohen-Jonathan, S. Marchais, H., Douziech-Eyrolls, L., Souce, M., Dubois, P and Chourpa, I. (2007). Comparative Study of Doxorubicinn-loaded Poly(lactide-co-glycolide) Nanoparticles Prepared by Single and Double Emulsion Methods. *European Journal of Pharmaceutics and Biopharmaceutics*. 66, 488–492.
- Thioune, O., Fessi, H., Devissageut, J. P., and Puisieux, F. (1997). Preparation of Pseudolatex by Nanoprecipitation: Influence of the Solvent Nature on Intrinsic Viscosity and Interaction Constant. *International Journal of Pharmaceutics*. 146, 233–238.
- Thomas, C., Pillai, L.S., and Krishnan, L. (2014). Evaluation of Albuminated Curcumin as Soluble Drug Form to Control Growth of Cancer Cells in Vitro. *Journal of Cancer Therapy*. 5, 723–734.
- Thommes, M. (2010). Physical Adsorption Characterization of Nanoporous Materials. *Chemie Ingenieur Technik*. 82(7), 1059–1073.
- Tourne-Peteilh, C., Begu, S., Lerner, D. A., Galarneau, A., Lafont, U. and Devoisselle, J. (2012). Sol-Gel One-Pot Synthesis in Soft Conditions of Mesoporous Silica Materials Ready for Drug Delivery System. *Journal of Sol-Gel Science and Technology*. 61,455–462.
- Vallet-Regi, M., Rámila, A., Real, R. P., and Pérez-Pariente, J. (2001). A New Property of MCM-41: Drug Delivery System. *Chemistry of Materials*. 13(2), 308–311.
- Wang, H. and Brown, H. R. (2004). Self-Initiated Photopolymerization and Photografting of Acrylic Monomers. *Macromolecular Rapid Communication*. 25, 1095–1099.
- Wang, S. (2009). Ordered Mesoporous Materials for Drug Delivery. *Microporous and Mesoporous Materials*. 117, 1–9.
- Wen, H. and Park, K. (2010). *Oral Controlled Release Formulation Design and Drug Delivery Theory to Practice*. New Jersey: John Wiley & Sons.
- Wilson, C. G. and Crowley, P. J. (2011). *Controlled Release in Oral Drug Deliver*. New York: Springer.
- Yin, T., Dong, L., Cui, B., Wang, L., Yin, L., Zhou, J. and Huo, M. (2015). Curcumin Entrapped Folic Acid Conjugated PLGA-PEG Nanoparticles Exhibit

Enhanced Anticancer Activity by Site Specific Delivery. *International Journal of Nanomedicine*. 10, 7397–7412.

Zharapova, L. (2012). *Synthesis of nanoparticles and nanocapsules for controlled release of the antitumor drug "Arglabin" and antituberculosis drugs*. Eindhoven: Technische Universiteit Eindhoven.

Zolnik, B.S. and Burgess, D.J. (2007). Effect of Acidic pH on PLGA Microsphere Degradation and Release. *Journal of Controlled Release*. 122, 338–344.