PREPARATION OF POLY(LACTIC ACID) (PLA) MICROSPHERES FOR DRUG DELIVERY SYSTEM

by

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LIST OF SYMBOLS

d_{max}	Maximum stable droplet Size
d_{32}	Sauter's mean diameter
D	Diameter of stirrer
ρ_c	Density of Continuous Phase
N	Stirring Speed
We	Weber Number
C_1	Coefficient of the correlation
C_2	Coefficient of the correlation
σ	Interfacial tension
μ_d	Viscosity of dispersed phase
μ_c	Viscosity of continuous phase
ϕ_d	Dispersed phase volume ratio
τ	Shear stress
μ	Eddy viscosity
γ	Shear rate
α	Coefficient that depend on many other factor
C_3	Coefficient of the correlation
C_4	Coefficient of the correlation
τ	Shear Stress
μ	Eddy Viscosity
γ	Shear Rate
ϕ_d	Volume Ratio of Dispersed Phase

$+ ve$	Positive
$- ve$	Negative
γ_{sv}	Interfacial energy between solid surface (*s*) and vapor (*v*)
γ_{sl}	Interfacial energy of solid and liquid (*l*)
γ_{lv}	Interfacial energy of liquid (*l*) and vapor (*v*)
θ	Water contact angle
γ_L^d	Dispersion forces of liquid surface tension
γ_L^P	Polar forces of liquid surface tension
A_1	Absorbance of first sample
A_2	Absorbance of the second sample
A_n	Absorbance of the *n* th sample
n	The number of sample
R	The extracted volume
W	The total weight of the model drugs
m	Slope of the graph
C	y-intercept of graph

LIST OF ABBREVIATIONS

PLA	Poly(lactic acid)
ESE	Emulsion and solvent evaporation
PSD	Particle size distribution
HCl	Hydrochloride acid
NaOH	Sodium hydroxide
DP	Dispersed phase
CP	Continuous phase
T	Turbulence flow
V	Viscous forces in laminar flow
C	Cavitation
L	Low
M	Moderate
H	High
B	Batch
C	Continuous
V	Viscous
N	Not so viscous
W	Aqueous
DPV	Dispersed phase volume
PLLA	Poly(L-lactic acid)
PLGA	Poly(lactic-co-glycolic)
PDLLA	Poly(D,L-lactic acid)
DCM	Dichloromethane

PVA	Poly(vinyl alcohol)
RhB	Rhodamine B
MO	Methyl Orange
SEM	Scanning electron microscopy
DCAT	Dynamic contact angle and tensiometer
UV-Vis	Ultraviolet-visible
XPS	X-ray photospectroscopy
DSC	Differential scanning calorimetry
Log P	Partition coefficient

PENYEDIAAN MIKROSFERA POLI(ASID LAKTIK) (PLA) UNTUK SISTEM PENGHANTARAN UBAT

ABSTRAK

Poli(asid laktik) (PLA) mikrosfera telah berjaya disediakan melalui kaedah emulsi dan pemeruapan pelarut (ESE). Taburan saiz partikel (PSD) mikrosfera yang diperoleh adalah dalam lingkungan 1 - 250 μm, merupakan lingkungan saiz yang boleh diterima bagi penghantaran jenis suntikan "parenteral". Kaedah "shake flask" dibuktikan sebagai teknik alternatif untuk menentukan kebolehlaksanaan pengkapsulan sesuatu ESE sistem. Dalam projek ini, pasangan pelarut diklorometana-air telah digunakan dalam sistem shake flask untuk mensimulasikan sistem ESE, dan Rhodamine B telah digunakan sebagai model ubat sepanjang projek ini. Parameter yang dikaji dalam fabrikasi mikrosfera adalah kepekatan PLA, kepekatan PVA dan nisbah isipadu fasa teragih (DP). Kesan parameter pada PSD, morfologi permukaan dan kecekapan pengkapsulan telah dinilai. Formulasi optimun adalah pada 25% DP, 15% PLA dan 1% PVA, yang mana hasil mikrosfera tertinggi diperolehi dengan penggunaan PVA terendah dalam ESE sistem dan taburan partikel saiz diperolehi dalam 1- 50 μm. Bagi formulasi ini, pembusaan emulsi telah diperhatikan semasa pengacauan dalam proses pengemulsian. Dicadangkan bahawa, titisan yang tersebar dalam emulsi lebih cenderung berada dalam struktur buih yang seterusnya memberikan kestabilan tambahan antara titisan atau partikel separuh keras tersebut. Teknik hidrolisis pengaruh pemangkin telah digunakan untuk mengubahsuaian permukaan mikrosfera. Kajian atas sifat-sifat permukaan dan pukal telah dijalankan untuk mengesahkan keberkesanan teknik hidrolisis. Secara keseluruhan, faktor-faktor termasuk skala masa, jenis pemangkin dan kepekatan pemangkin harus dimanipulasi untuk mendapatkan sifat permukaan yang dikehendaki (contohnya, hidrofilik, caj dan morfologi permukaan) dengan ubah bentuk sifat pukal mikrosfera yang minimum.

PREPARATION OF POLY(LACTIC ACID) (PLA) MICROSPHERES FOR DRUG DELIVERY SYSTEM

ABSTRACT

Poly(lactic acid) (PLA) microspheres were fabricated through emulsion and solvent evaporation (ESE) technique. The particle size distributions (PSD) of microspheres obtained were in the range of 1- 250 µm, as within the range of acceptable size in parenteral injection. A shake flask method was demonstrated as an alternative technique to determine the encapsulation feasibility of an ESE system. Herein, dichloromethane-water solvent pair was used in shake flask system in order to simulate ESE system, and Rhodamine B was utilized as model drug throughout the project. In the fabrication of microspheres, the studies parameters were included PLA concentration, PVA concentration and dispersed phase volume ratio (DP). The effect of parameters on PSD range, surface morphology and encapsulation efficiency were evaluated. The optimum formulation was at 25 % DP, 15 % PLA and 1 % PVA, wherein the highest output of microspheres obtained at lowest PVA consumption in the system and narrow PSD obtained in range 1- 50 µm. In this formulation, extensive foaming of emulsion was observed during the emulsification process. It was suggested that the dispersed droplets tends to stay within the foam structure which further provide extra stabilization between droplets or partial solidified particles. The surfaces of microspheres were modified through catalytic induced hydrolysis technique. The surface and bulk properties of treated microspheres were investigated to verify the effectiveness of hydrolysis technique. Results demonstrated that the factors included timescale, type of catalyst and concentration should be manipulated in order to obtain the desired surface properties (e.g. hydrophilicity, surface charges and surface morphology) with minium deformation in microspheres bulk propertie

Chapter 1

Introduction

1.1 Overview

Drug delivery system is defined as the device which encapsulated with specific amount of drug further delivery it in a controlled or sustained manner upon the administration. In pharmaceutical, it is urged to have the suitable drug delivery system that able to maintain the blood drug concentration lies between the minimum effective and maximum toxic concentration (Uchizono, 2006, Liechty *et al*., 2010). In order to deliver drugs to diseased site in the body in a more effective and less invasive way, a new dosage form technology of drug delivery has emerged in the late 1960's (Coelho *et al.*, 2010).

There are variable approached in designing an effective drug delivery system by using polymeric materials either in natural or synthetic forms. One of the promising design is used of biodegradable microspheres prepared from polyester, such as poly(lactic acid) (PLA), poly(glycolic acid) and their copolymer poly(lactic-co-glycolic). They are mostly focusing on the encapsulation of large molecules, e.g., peptides, proteins and plasmid Deoxyribo Nucleic Acid (DNA) for potential used as vaccines or as long-acting release drug formulation. The major advantages of biodegradable systems are they was eventually absorbed or excreted by the body. The drug release of microspheres was controlled by the polymer degradation rate and particle size of microspheres (Ulery *et al.*, 2011). One of the major considerations in microspheres fabrication was the particle size distribution as it determined the drug administration route, drug release properties, patient compliance and safety during the application period (Berkland *et al.*, 2002).

Drug loaded microspheres are prepared through microencapsulation technique. Microencapsulation, is the term used to describe the technique to surround or coat certain chemical entity (in the form of either solids, liquids or gaseous) within a material that able to release the contents at certain conditions (upon moisture, pH, physical force or combination thereof) (Luzzi, 1970, Chanana *et al.*, 2013). It has been reported that emulsion and solvent evaporation technique is most successful to load either insoluble or poorly soluble drugs in biodegradable microspheres (O'Donnell and McGinity, 1997). The effectiveness of microspheres preparation technique for drug delivery usage is depends on the successful entrapment of the drug within the particles. The understanding ESE technique from the aspect of intrinsic (interaction between materials) and extrinsic (adjustable parameters such as stirring speed, water-in-oil phase ratio, drug loading, polymer and stabilizer concentration) are crucial in order to produce microspheres with desired drug encapsulation.

Another consideration involved in designing an effective drug delivery system is the surface properties of microspheres. Generally, the surfaces of polyester based biodegradable microspheres are recognized as non-biocompatible because of hydrophobic in nature and lacking of bio-recognized functional group or molecules. These might cause rapid elimination of microspheres in the biological system prior drug release from microspheres (Stolnik *et al.*, 1995). Material surfaces can be modified by a variety of different methods, such as the application of a surface chemical gradient, self-assembled films, surface-active bulk additive and surface chemical reaction. Microspheres surfaces are required to be modified with various functional groups such as methyl-, hydroxyl-, amino-, and carboxyl, all of which can be found on natural biological surfaces in order to optimize the function of microspheres as drug delivery system (Roach *et al.*, 2007).

1.2 Problem Statements:

Emulsion and solvent evaporation (ESE) was selected as microspheres fabrication technique, because this technique is conceptually simple in experimental setup. However, the quality of microspheres (e.g. particle size, drug loading, agglomerate and etc.) prepared from this technique are highly dependent on the system nature. Despite the widespread use of this technique, encapsulation methodologies are still largely based on trial and error. More quantitative theory and experiments are required to improve our understanding of how the encapsulation conditions affect the final particle characteristics. Therefore, at the preliminary stage of microsphere fabrication the establishment and understanding of ESE technique are required.

The encapsulation feasibility of the ESE process is highly dependent on the materials interaction and the materials' properties. As illustrated in Fig. 1.1, the feasibility of the system to encapsulate certain chemical substance in PLA microspheres can only be determined if the series of ESE process was run and the obtained microspheres were characterized. Therefore, an alternative approaches was proposed to determine the encapsulation feasibility to eliminate this trial-and-error procedure. In this research, a shake flask method was proposed to tackle this issue. In this shake flask approach, if the drug has higher affinity toward the polymer's solvent in shake flask system, then this drug is able to be encapsulating within the microspheres in through ESE technique.

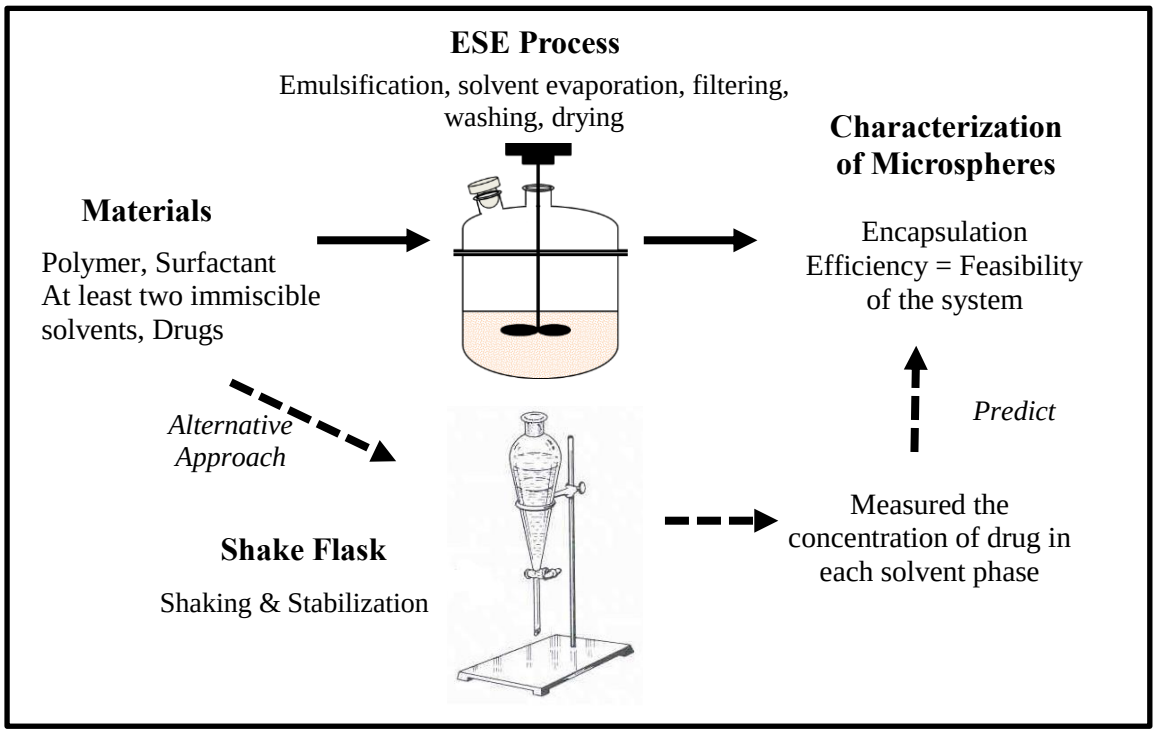

Fig. 1.1: Shake flask method proposed to replace the ESE processes during the determination of encapsulation feasibility

Particle size distribution of microspheres is crucial in drug delivery purposes. Unfortunately, the main issue of using the ESE technique in microspheres fabrication was the broad particle size distribution. Various approaches have been conducted to narrow the PSD, through either high stirring forces by homogenizer and sonication, or through highly controllable electrohydrodynamic atomization and membrane emulsification (Liu *et al.*, 2011, Vauthier and Bouchemal, 2009, Pareta and Edirisinghe, 2006, Sawalha *et al.*, 2008). However, the mentioned modified techniques are required extra machinery setup or exposed the risk of emulsion heat up that induces the deterioration of drug (Freitas *et al.*, 2005). Therefore, it is desired to improve the ESE system which able to narrow the particle size distribution without possessing any difficulty in either the fabrication process or drug deterioration.