A STUDY OF POLYCAPROLACTONE PARTICLES PREPARED USING ULTRASONICATOR VIA TWO STEP SOLVENT EVAPORATION METHOD

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DECLARATION

I declare that this thesis entitled "A Study of Polycaprolactone Particles Prepared Using Ultrasonicator Via Two Step Solvent Evaporation Method" is the results of my own research except as cited in the references.

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Kajian mengenai Polycaprolactone partikel disediakan menggunakan ultrasonikator melalui kaedah penyejatan pelarut dua langkah.

ABSTRAK

Salah satu polimer sintetik yang telah digunakan secara meluas dalam aplikasi bioperubatan adalah PCL. Walau bagaimanapun, saiz mikropartikel PCL yang berbeza menghasilkan pelbagai jenis aplikasi. Oleh itu, objektif utama kajian ini adalah untuk menyelidiki kesan pelbagai parameter pemprosesan ke atas saiz zarah dan ciri-ciri mikropartikel polikaprolakton (PCL) yang boleh digunakan dalam pelbagai aplikasi. Parameter yang digunakan dalam kajian ini adalah nisbah air-minyak (w/o), kadar pemakanan, amplitud, dan berat molekul PCL. Kaedah penyediaan yang digunakan adalah kaedah penyejatan menggunakan penyegerak ultrasonik untuk menghasilkan saiz zarah yang kecil. Dalam kajian ini, mikroskop optik digunakan untuk mengamati saiz mikropartikel PCL. Didapati saiz mikropartikel menunjukkan peningkatan dari 0.94 µm hingga 0.99 µm kerana diikuti oleh peningkatan jumlah fasa minyak. Bagi kadar pemakanan, saiz mikropartikel yang diperoleh meningkat dari 0.84 µm hingga 1.11 µm untuk nisbah 3:7 dan dari 0.90 µm hingga 1.07 µm untuk nisbah 7:3 apabila menggunakan pemakanan yang berbeza dari 0.5ml/min hingga 4ml/min. Walau bagaimanapun, apabila amplitud penyegerak ultrasonik meningkat, saiz mikropartikel yang terbentuk berkurang, untuk nisbah 7:3 dari 1.04 µm hingga 0.94 µm, untuk nisbah 5:5 dari 1.05 µm hingga 0.92 µm dan untuk nisbah 7:3 dari 0.98 µm hingga 0.79 µm, disebabkan oleh tenaga geseran yang lebih tinggi untuk menghasilkan larutan mikropartikel emulsi semasa proses emulsifikasi. Terakhir, bagi berat molekul PCL, saiz mikropartikel yang diperoleh meningkat kerana 80,000 kg/mol, iaitu berat molekul yang lebih tinggi, boleh menghasilkan saiz zarah yang lebih besar. Kesimpulannya, parameter memainkan peranan utama semasa penyediaan mikropartikel PCL, memudahkan pelbagai jenis aplikasi.

Kata kunci: Polycaprolactone (PCL), Mikropartikel, Kaedah Penyedutan Pelarut, Ultrasonicator probe.

A study of polycaprolactone particles prepared using ultrasonicator via two step solvent evaporation method.

ABSTRACT

One synthetic polymer that had seen extensive usage in biomedical applications was PCL. Nonetheless, differing PCL microparticle sizes resulted in diverse application types. Therefore, the main objective of this study was to investigate the effect of various processing parameters on particle size and the characteristics of polycaprolactone (PCL) microparticles that could be used in various applications. The parameters used in this study were water-oil ratio (w/o), feeding rate, amplitude, and molecular weight of PCL. The preparation method used was the solvent evaporation method using ultrasonicator probe to produce a small particle size. In this study, an optical microscope was used to observe the size of PCL microparticles. It was found that the size of the microparticles showed an increase from 0.94 µm to 0.99 µm because it was followed by increasing amounts of the oil phase. For feeding rate, the size of the microparticles obtained increased from 0.84 µm to 1.11 µm for 3:7 ratio and from 0.90 µm to 1.07 µm for 7:3 ratio when using different feedings from 0.5ml/min to 4ml/min. However, when the amplitude of the ultrasonicator probe increased, the size of the microparticles formed decreased, for 7:3 ratio from 1.04 µm to 0.94 µm, for 5:5 ratio from 1.05 µm to 0.92 µm and for 7:3 ratio from 0.98 µm to 0.79 µm, due to the higher shear energy to produce emulsion microparticle solution during the emulsification process. Lastly, for the molecular weights of PCL, the size of the microparticles obtained increased because 80,000 kg/mol, i.e., the higher molecular weights, could produce a larger particle size. In conclusion, parameters played a major role during the preparation of PCL microparticles, facilitating various types of applications.

Keywords: Polycaprolactone (PCL), Microparticles, Solvent Evaporation method, Ultrasonicator probe.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Microparticles or microspheres are known as small particles having sizes between a few nanometers to a few micrometres. Microspheres and microcapsules are two different forms of microparticles. Microspheres are systems based on matrices, while microcapsules are made up of a core substance that is entirely encased in a polymeric film (Maqbool et al., 2019). They are frequently used in a variety of fields such as medicine, electronics, environmental science, and materials science because of their special qualities and numerous uses. These particles may be made of many substances, including polymers, metals, ceramics, or biological components (Yadav et al., 2023).

Biodegradable polymer is one of the popular materials used in the preparation of microparticles because of their compatibility with biological systems. These polymers can be designed to have specific properties such as controlled release of compounds that are encapsulated or degradation rates that are matched to the desired release profile. This makes them the perfect candidate for targeted medication delivery, in which therapeutic substances may be delivered to a particular region in the body via microparticles, which release the drug in the body gradually over time (Manuscript, 2014).

In this study, Polycaprolactone (PCL) was used to prepare the microparticle through the two-step solvent evaporation method using an ultrasonicator probe. Not similar to polylactide (PLA) or polyglycolide (PLG), PCL is an aliphatic polyester polymer that is both biocompatible and biodegradable. It however degrades slowly and does not generate an acidic environment. In addition to that, the administration of active drugs may be possible despite the limited permeability of macromolecules in PCL (Kim et al., 2009). Solvent evaporation method was used in this study because it is the method for producing polymeric particles that is most commonly employed. This adaptable method guarantees the intended release profile and allows for the inclusion of several active medicinal components in polymeric matrices (Urbaniak & Musiał, 2019).

1.2 Problem Statement

The size range of microparticles is 0.1 to 100 µm. For use in biomedical and drug delivery systems, their variety of sizes endows them with several advantageous qualities. These particles can be produced in several ways, but most of them require creating an emulsion to include bioactive compounds (Willerth, 2017). The various sizes of the microparticles lead to various application types. For example, for capsules, the size meters to know the volume they can contain while for particles for tissue engineering, there are different pore size shapes (Luciani et al., 2008).

Hence, the purpose of this research is to prepare a wide range of sizes and microsphere types by using parameters such as water-oil ratio (w/o), feeding rate and amplitude by using a solvent evaporation method. Due to its simplicity of use, ease of scaling up, and reduced residual solvent potential compared to other procedures, the solvent evaporation method has garnered the greatest interest (Hwisa et al., 2013). In

this study, we use two-step solvent evaporation with an ultrasonicator to get the hollow microparticles.

1.3 Objectives

The following will be the study's objectives such as:

1. To prepare microparticles using one of polymer, which is Polycaprolactone (PCL).
2. To investigate the effect of various processing parameters on particle size and the characteristics of microparticles.

1.4 Scope of Study

This study focuses on the preparation of microparticles using Polycaprolactone (PCL) and varying processing parameters on particle size such as to look at the size and type, as well as the characteristics of microparticles by solvent evaporation method. Even though there has been much research in this field, more attention has been focused on nanoparticles than microparticles, leaving several unanswered questions. This is because not all applications use nanoparticles while microparticles can also be used in many applications. For example, fertilizers can be made from microparticles and do not require much cost compared to nanoparticles which will cost a lot.

1.5 Significances of Study

Hence, the purpose of this research is to prepare a wider range of sizes and microsphere types by using parameters such as water-oil ratio (w/o), feeding rate and

amplitude by using solvent evaporation method. The solvent evaporation method to create microparticles is an inexpensive method to be used in various fields such as in medicine for capsule-control release particles. In tissue engineering as scaffolds, it can also developed as a sensor in field such as in biomaterials development. The creation of PCL microparticles can be increased for commercial applications by optimizing this process.

CHAPTER 2

LITERATURE REVIEW

2.1 Microparticles

Polymeric microparticles are spherical particles with average diameters of 1-1000 μm that are created by a polymer matrix. Polymeric microparticles with customized morphologies (such as shape, size, size distributions, and porosity) and unique characteristics may be designed and manufactured with particular function for a variety of advanced applications. In a variety of applications, such as the drug delivery, cosmetics, environmental remediation, and materials science, functionalized polymeric microparticles have considerable significance and promise (Ju & Chu, 2019).

Microparticles provide advantages in the field of drug delivery, including controlled release, increased bioavailability, and targeted administration of medicinal substances (Bale et al., 2016). Microparticles are widely used in cosmetics as well. The stability and effectiveness of the active substances can be improved by using these particles as transporters. It is possible to give controlled release of cosmetic components, allowing for longer action on the skin or hair, by using microparticles with specified features, such as regulated porosity or surface changes (Hwang et al., 2020). Microparticles provide ways to cleanse water and reduce pollutants in environmental cleanup. They can be functionalized to selectively adsorb and filter out pollutants from water sources, such organic pollutants, or heavy metals. High surface area-to-volume ratio microparticles offer superior adsorption capabilities (Zhang et al., 2018).

Microparticles are used in materials science to create sophisticated materials with specific features. They can be used to provide certain properties, such increased mechanical strength, thermal stability, or electrical conductivity, to coatings, composites, or functional materials. Microparticles are employed in additive manufacturing as well, where they may be used as reinforcements or fills to improve the qualities of 3D-printed items (Kamyshny & Magdassi, 2019).

2.1.1 Type of Microparticles

Microspheres and microcapsules are the two different forms of microparticles. Microcapsules are core-shell microparticles with a core that might be solid, liquid, or even empty spaces. Microspheres are defined as microparticles made of a homogenous and solid polymer matrix (Ju & Chu, 2019). A wide variety of active chemicals can either be encapsulated inside the microcapsules or disseminated throughout the polymer matrix of the microspheres (Ju & Chu, 2019). Microparticles offer various benefits, including the ability to hide harsh tastes, preserve volatiles, lessen drug adverse effects, and improve drug targeting. There are certain limitations, too, including stricter quality control and greater product prices brought on by excipients that are more expensive or because the equipment and procedures are more advanced (Lengyel et al., 2019).

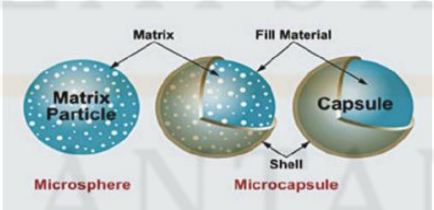


Figure 2.1: Different micro-particle structures

Source: (Manjanna et al., 2010)

2.2 Materials used to produce microparticles.

Depending on their intended function, microparticles can be created from several materials such as polymers, metals, ceramics, glass and other substances (Mahato, 2017). Polymer is one of the most extensively used to create microparticles. For polymer materials, it can use biodegradable polymer materials, especially for use in biomedical applications. In the creation of microparticles, the most popular polymers compared to others include Poly (lactic acid) (PLA), Poly (methyl methacrylate) (PMMA) and Polycaprolactone (PCL). The preparation process, benefits, and limitations of those polymers for the creation of microparticles are covered in the section that follows.

2.2.1 Poly (lactic acid)

A biodegradable polyester known as Poly (lactic acid) (PLA) is created from monomers taken from plentiful natural resources like cornflour and regenerated sugarcane. The most common way to make PLA is by a technique called ring opening polymerization (ROP), which includes solvents like diphenyl ether, chloroform, and toluene as well as a variety of catalysts like zinc, tin, lead, and aluminium, initiators including sec-, -n, and tert-butyl lithium, and many kinds of catalysts like zinc, tin, lead, and aluminium. By controlling the residence time, catalyst type, consternation, and temperature, ring opening polymerization may produce polymers with different molecular weights (Balla et al., 2021). The capacity to construct a range of structures with the right mechanical characteristics, topography, geometry, and architecture as required for various biomedical applications has been a benefit of PLA-based

biomaterials. The fabrication of PLA-based goods using fibres spun from polymer melt or solution is one of the oldest processes. Solution spinning technologies have also been widely used to create fibres for biomedical purposes since PLA is soluble in a variety of solvents. Historically, spinning PLA-based fibres into mono- and multi-filament sutures was the method used, but now that PLA has been replaced by other aliphatic polyesters like PGA due to its slower rate of degradation. Orthopaedic uses for woven, knitted, and braided constructions made from spun fibres include the regeneration of cartilage, ligaments, and bone (Narayanan et al., 2016).

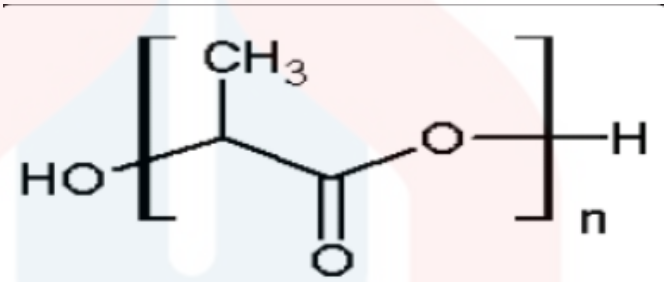


Figure 2.2: Chemical structure of PLA

Source: (Mahapatro & Singh, 2011)

2.2.2 Poly (methyl methacrylate)

Poly (methyl methacrylate) (PMMA) is a thermoplastic polymer that may be created from its monomer utilising a variety of polymerization methods, such as bulk, solution, suspension, and emulsion procedures employing free radical and anionic initiations. Due to the nearby methyl group (CH3) on its backbone preventing it from packing tightly in a crystalline form, PMMA exhibits an amorphous microscopic structure. It has several very advantageous qualities, including a high Young's modulus and a low elongation at break, as well as great chemical stability, biocompatibility, nontoxicity, and good

mechanical characteristics (Ahangaran et al., 2019). PMMA provides several benefits, including outstanding aesthetic qualities, appropriate strength, simplicity in manufacture, ease of repair, and minimal water absorption and solubility. The polymerization shrinkage, poor impact strength, limited fatigue resistance, and weak flexural properties of PMMA were some of its disadvantages (Sheng et al., 2018).

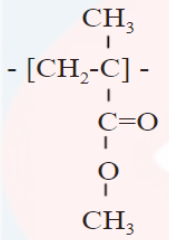


Figure 2.3: Chemical structure of PMMA

Source: (Hogabri et al., 2009)

2.2.3 Polycaprolactone

Ring-opening polymerization of -caprolactone monomers yields Polycaprolactone (PCL), a semicrystalline ester polymer. Due to its crystalline structure, which makes it easily formable at relatively low temperatures, PCL has a glass transition temperature (Tg) of around 60 °C and a melting point that ranges from 59 to 64 °C. Due to its numerous benefits, including biodegradability, high strength, and biocompatibility, PCL has drawn a lot of interest among other types of biopolymers. It is resistant to chlorine, solvents, oil, and water. This polymer is widely renowned for its biodegradability and noticeably slower degradation. Due to its slow rate of degradation, PCL is frequently employed as a material in drug delivery systems that have an active duration of over a year. A bio scaffold use for the material is also mentioned. In

terms of potential biomedical usage, PCL is a superior polymer than PLA or PGA due to its biodegradability, permeability, and inability to create an acidic environment. Additionally, PCL may be used to release drugs over extended periods of time, even a year, due to its low rate of degradation as compared to PLA and PGA. Unfortunately, the commercialization of PCL has been limited because to its difficult and costly manufacturing. The substance's hydrophobic surface also contributes to how poorly it sticks to cells. Additionally, PCL solvents are known to be toxic, which poses a risk to human health. Another disadvantage of the material's low melting point is that it prevents use in applications where greater temperatures are present (Faiz et al., n.d.).

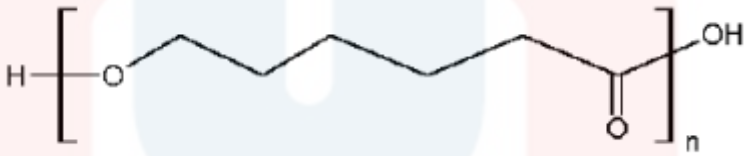


Figure 2.4: Chemical structure of PCL

Source: (Mahapatro & Singh, 2011)

In summary, Polycaprolactone (PCL) is a semicrystalline ester polymer with a glass transition temperature of 60 °C and a melting point of 59 to 64 °C. It has numerous benefits, including biodegradability, high strength, and biocompatibility. It is used in drug delivery systems and bio scaffolds.

2.3 Method used to produce microparticles.

Microparticles made from biodegradable polymers have been produced using a variety of processes. Depending on the characteristics of the polymer, particle size,

material, and application, a specific process is used. Previous studies have suggested several ways to prepare microparticles, including spray drying, hot melting, and solvent evaporation. The technique specifications, benefits, and limitations of those methods used to create PCL microparticles have been covered in the section below.

2.3.1 Spray Drying Method

A popular method for producing particles, spray drying involves turning a fluid substance into dried particles by utilising a gaseous hot drying agent (Santos et al., 2018). The creation of particles during the spraying process has received a lot of attention lately. These efforts have led to the use of spray technology to the production of particles to produce a variety of goods, from microencapsulated flavours to pharmaceutical direct compression excipients and/or granulations. The most used industrial procedure for creating and drying particles is spray drying. It is well suited for the continuous synthesis of dry solids from liquid feedstocks in the form of solutions, emulsions, and pumpable suspensions in powder, granulate, or agglomerate form. Spray drying is the best procedure when the finished product needs to meet exact quality requirements for particle size distribution, residual moisture content, bulk density, and particle shape. The primary benefit of spray drying is the technology's exceptional adaptability, which is seen when examining the variety of applications and products that may be produced. Spray drying has a variety of options that no other drying process can match, including the ability to produce large, agglomerated powders for oral doses, extremely small particles for pulmonary administration, amorphous to crystalline products, and the possibility for one-step formulations. Because of its adaptability and

repeatability, spray drying is a popular industrial drying method (Gohel et al., 2009).

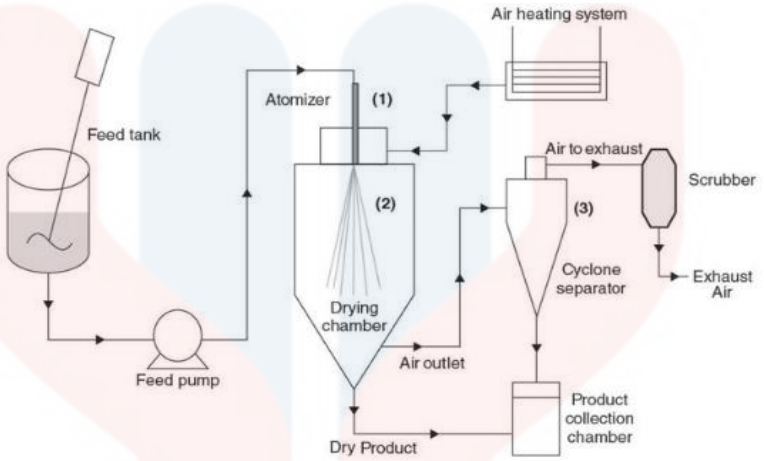


Figure 2.5: Schematic diagram of spray drying process.

(Source: (Santos et al., 2018))

2.3.2 Hot Melting Method

When making solid dosage forms including tablets, granules, pellets, and microparticles using hot-melt techniques, molten or softened materials are used as binders. These materials are also used to coat pharmaceutical formulations. Depending on the materials used, the processes enable the creation of either immediate or controlled release dosage forms. Appropriate polymers, waxes, or other lipid-based compounds can all be used as meltable materials. During the formulation process, these materials are melted, and they solidify during or after the technical process. One of the main benefits of this strategy is that there are no solvents used in the formulation preparation (Homar et al., 2011). Additionally, using such a procedure prevents residual solvent problems, which are particularly difficult with organic solvents. Hot-melt extrusion, hot-melt agglomeration in high-shear mixing, and creation of

straightforward melt dispersions are the most often used techniques (Homar et al., 2011).

2.3.3 Solvent Evaporation Method

The solvent evaporation method is an adaptable method for creating polymeric particles. It is based on the evacuation of the volatile organic phase from the o/w emulsion, which causes the water-insoluble particles to solidify. Studies and reviews have been conducted to modify the solvent evaporation method to allow for more effective drug loading. Hydrophilic medicines can be included into w/o/w solvent evaporation method by adding a second water phase, while in s/o/w solvent evaporation method, a different method of hydrophilic drug inclusion in the form of suspension in organic phase was accomplished (Urbaniak & Musiał, 2019). Emulsions are created by formulating polymer solutions in volatile solvents, such as dichloromethane and chloroform. On evaporation of the polymer's solvent, the emulsion transforms into a suspension of microparticles. Traditional methods involve ultrasonication or high-speed homogenization, followed by solvent evaporation. To remove additives, microparticles can be recovered by ultracentrifugation and rinsed with distilled water (K et al., 2017).

Rotor-stator homogenizers are widely employed in laboratory-scale facilities. The final shape and size of the drug carrier is influenced by homogenization settings, the content of homogenised two-phase systems, the capacity to inhibit droplet coalescence, the volume and form of the homogenizer vessel, and the geometry of the homogenising tip. In silico simulations have established the importance of shear stress and eddies as homogenization

variables, but practical evaluation of parameters still outperforms theoretical prediction (Urbaniak & Musiał, 2019). Ultrasonication (US) is the application of ultrasound at low temperature. As a result, it can be utilised for temperature-sensitive items where there is a worry about nutritional loss, such as vitamin-C loss, protein denaturation, non-enzymatic browning, etc. However, stable enzymes and/or bacteria that could demand a lot of energy must be killed or rendered inactive over an extended period. Depending on the ultrasound strength and duration of application, there may be an increase in temperature during ultrasound application; this needs to be controlled to optimise the process (Ravikumar, 2017).

Overall, solvent evaporation method is the easiest method to create polymeric particles and many people use this method to make microparticles.

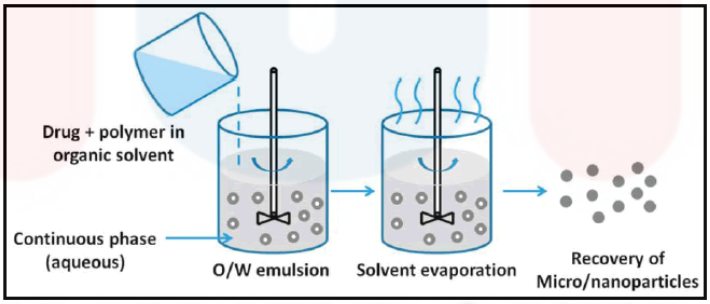


Figure 2.6: Preparation of microparticles by Solvent Evaporation process.

(Source: (Wang et al., 2016))

In general, although there are several techniques for creating microparticles, spray drying, hot melting, and solvent evaporation are the most often employed. The best way to use it depends on the requirements of the application, and each strategy has its own benefits and drawbacks (Prashant et al., 2011).

2.4 The solvent evaporation method using ultrasonicator probe

In this study, an ultrasonicator probe has been used to help the emulsion of microparticles in the solvent evaporation process. By using an extremely high frequency of sound energy, an ultrasonicator probe may create microparticles and nanoparticles. Furthermore, previous research also agreed with it, compared to methods that use homogenizers, ultrasound emulsification is a more efficient way to create a microsphere (Iqbal et al., 2015). PCL microparticles were made via ultrasound-assisted solvent evaporation. It has been shown that, in comparison to homogenizers, ultrasonication may generate more homogenous emulsion, have smaller droplet sizes, and are more stable.

2.5 Importance of particle size

Due to its profound influence on their characteristics and behaviour, microparticle size is crucial in many scientific and commercial sectors. Since microparticles generally have sizes between 1 and 1000 micrometers, they display distinctive properties at this scale, which opens a wide range of possibilities. The capacity to modify a microparticle's qualities, including surface area, porosity, reactivity, dispersibility, and stability, has a direct impact on how well it functions and performs in a variety of applications. Across many scientific and industrial sectors, the size of microparticles is a crucial factor that influences their characteristics and performance. The creation and development of materials, medication delivery methods, and other applications are made possible by precise control over microparticle size, which results in enhanced performance and customized features (Champion et al., 2007).

2.6 Oil phase ratio

The amount of oil in a system divided by the volume of the dispersed phase (solid or hollow microparticles) is known as the oil phase ratio. It reveals the amount of oil to solid or hollow microparticles that are present. The volume fraction of oil in a system is determined by the oil phase ratio.

Although solid and hollow microsphere composites have drawn a lot of attention as solar reflectors or selective emitters, the mechanics behind their optical characteristics are still not entirely understood. Solid and hollow microspheres with diameters ranging from 0.125 μm to 8 μm have solar reflectance in the 0.4–2.4 μm wavelength range. Higher solar reflectivity results from hollow microspheres with thinner shells because they scatter light more effectively than solid microspheres. Low-refractive-index materials can have a high solar reflectivity due to the hollow microspheres' high scattering efficiency, which is caused by the contrast in refractive indices and the huge interface density. Strong backscattering in the electric field is the result of variable diameter (Yu et al., 2020).

Figure 2.7: Solid microparticle to hollow microparticles

(Source: (Park et al., 2018))

CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

Among the materials that will be used in this study are Polycaprolactone (PCL) (Mw = 80,000 kg/mol and 45,000 kg/mol) as a polymer material, polyvinyl alcohol (PVA) as a surfactant and dichloromethane (DCM) used as an organic solvent. All materials has been purchased from Sigma-Aldrich, Germany.

3.2 Methods

In this study, microparticles were prepared using an ultrasonicator using the two-step solvent evaporation method. The first step was to create a w/o emulsion with water to oil phase volume ratio of 1:9. In comparison to the oil phase contains 0.3g of 80 000 kg/mol PCL and 30ml of DCM (1%wt), 2ml per minute will be added into the oil phase, which comprises 0.35g of PVA and 70ml of distilled water (0.5%wt) using syringe pump. By applying high energy to an ultrasonicator probe with a 70% amplitude in 20 minutes, this immiscible fluid was being transformed into an emulsion. 5 second run, 5 second halt pulses were previously utilised. A rotary evaporator would be used to dry the microparticle emulsion solution after it had been created.

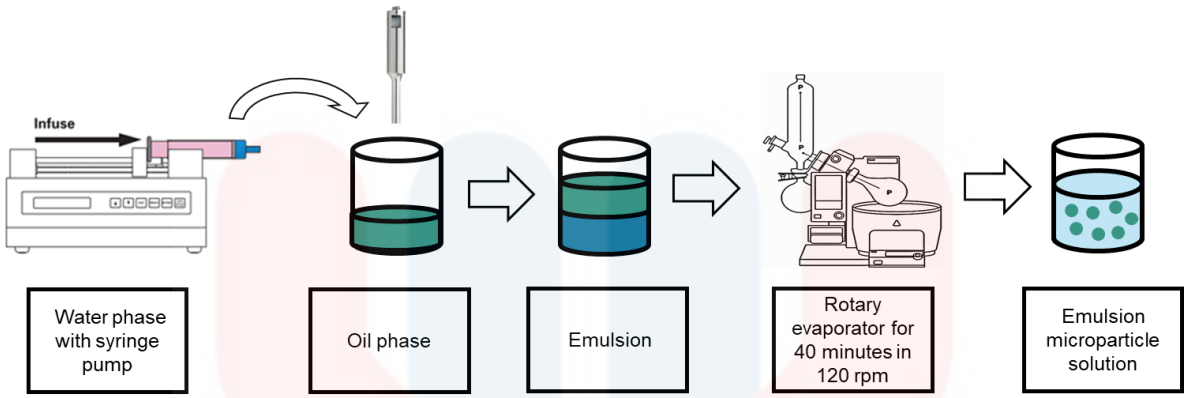


Figure 3.1: Schematic diagram of PCL microparticles preparation via solvent evaporation process using ultrasonicator probe.

The following parameters were altered during the processing of PCL microparticles which is w/o ratio (1:9, 3:7, 5:5 and 7:3); feeding rate of syringe pump (0.5ml/min, 2ml/min and 4ml/min) and amplitude of ultrasonicator probe (55%, 70%, and 85%). The parameters have been summarized in Table 1. To regulate the rate at which the solvent evaporates throughout the evaporation process, a rotating evaporator has been used. The solvent evaporation rate was regulated for the evaporation process using a rotary evaporator at a speed of 120 rpm for 40 minutes at 39°C. Following a brief explanation of the characterisation method, the emulsion solution will be examined using an optical microscope, as briefly described in the characterization process.

Table 3.1: Table of parameter

Sample	Water : Oil Ratio	Feeding Rate (ml/min)	Amplitude (%)	Concentration of surfactant (wt%)
1:9/(2ml/min)/70%	1:9	2ml/min	70	0.5
3:7/(2ml/min)/70%	3:7	2ml/min	70	0.5
5:5/(2ml/min)/70%	5:5	2ml/min	70	0.5
7:3/(2ml/min)/70%	7:3	2ml/min	70	0.5
3:7/(2ml/min)/55%	3:7	2ml/min	55	0.5
5:5/(2ml/min)/55%	5:5	2ml/min	55	0.5
7:3/(2ml/min)/55%	7:3	2ml/min	55	0.5
3:7/(2ml/min)/85%	3:7	2ml/min	85	0.5
5:5/(2ml/min)/85%	5:5	2ml/min	85	0.5
7:3/(2ml/min)/85%	7:3	2ml/min	85	0.5
3:7/(0.5ml/min)/70%	3:7	0.5ml/min	70	0.5
3:7/(4ml/min)/70%	3:7	4ml/min	70	0.5
7:3/(0.5ml/min)/70%	7:3	0.5ml/min	70	0.5
7:3/(4ml/min)/70%	7:3	4ml/min	70	0.5

3.2.1 Characterisation of microparticles

a) Optical microscope

Emulsion microparticle solution was seen using an Optical Microscope. A dropper was used to place one drop of PCL microparticle solution on top of the glass slide to prepare the sample for optical microscope observation. To effectively evaluate the picture of the emulsion microparticles, the observation procedure will start at a lower magnification (4x magnification) and progress to a greater magnification (40x magnification).

b) Particle sizing

Next, Image J will be used for calculating the pictures obtained with the optical microscope camera for microparticle size analysis. Next, a graph showing the particle size of PCL microparticles that observed in the range of 150 - 200 microparticles was created using Microsoft Excel and Origin software to analyse the microparticle solution.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Introduction

This chapter discussed the results obtained from various parameters, namely the size of PCL microparticles. The aim was to determine the effect of parameters on the size of PCL microparticles that were affected due to changes in these parameters.

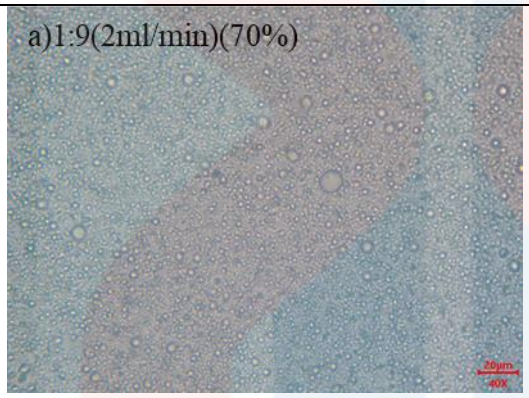
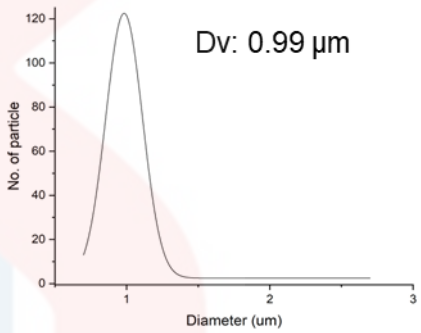
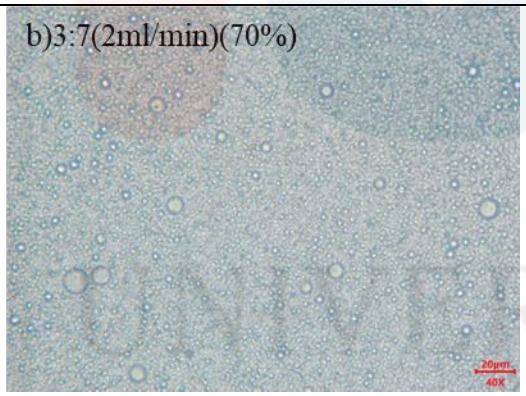
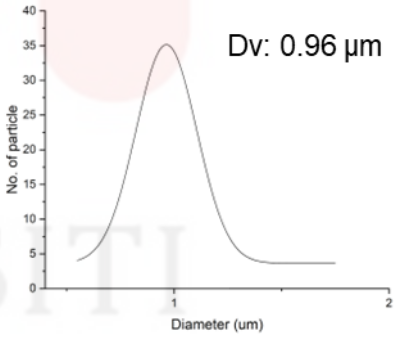
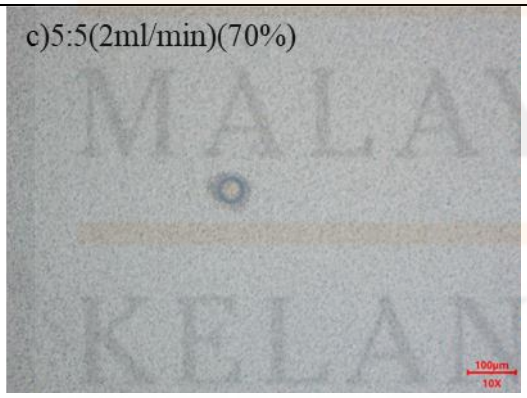
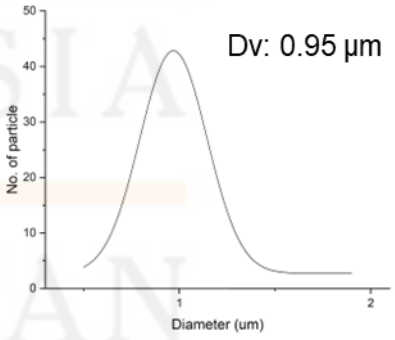
Table 4.1 shows the sizes of microparticles obtained from different ratios of water to oil phase, feeding ratio, and amplitude. Here, the images of microparticles observed under an optical microscope were calculated and analyzed. From the table, it was evident that the largest microparticles were obtained at a 3:7 w/o ratio with a feeding rate of 4 millilitres per minute, measuring 1.11 µm. On the other hand, the smallest size of microparticles, with a 7:3 w/o ratio at an amplitude of 85%, was 0.79 µm. Factors that could affect the size of microparticles were explained in the next sub-chapter.

Table 4.1: Size of PCL 80 microparticle

Sample	Water : Oil Ratio	Feeding Rate (ml/min)	Amplitude (%)	Concentration of surfactant (wt%)	Average diameter (Dv) (µm)
1:9/(2ml/min)/70%	1:9	2ml/min	70	0.5	0.99
3:7/(2ml/min)/70%	3:7	2ml/min	70	0.5	0.96
5:5/(2ml/min)/70%	5:5	2ml/min	70	0.5	0.95
7:3/(2ml/min)/70%	7:3	2ml/min	70	0.5	0.94
3:7/(2ml/min)/55%	3:7	2ml/min	55	0.5	1.04
5:5/(2ml/min)/55%	5:5	2ml/min	55	0.5	1.05
7:3/(2ml/min)/55%	7:3	2ml/min	55	0.5	0.98
3:7/(2ml/min)/85%	3:7	2ml/min	85	0.5	0.94
5:5/(2ml/min)/85%	5:5	2ml/min	85	0.5	0.92
7:3/(2ml/min)/85%	7:3	2ml/min	85	0.5	0.79
3:7/(0.5ml/min)/70%	3:7	0.5ml/min	70	0.5	0.84
3:7/(4ml/min)/70%	3:7	4ml/min	70	0.5	1.11
7:3/(0.5ml/min)/70%	7:3	0.5ml/min	70	0.5	0.90
7:3/(4ml/min)/70%	7:3	4ml/min	70	0.5	1.07

4.2 Effect of w/o ratio to the size of microparticle

Figure 4.1 shows that the size of microparticles increased when the ratio increased. Results obtained also showed similar trends as those obtained from a previous study.

Water : Oil ratio	Microparticles of PCL (40x magnification)	Graph for size distribution of microparticles of PCL
1:9		
3:7		
5:5		

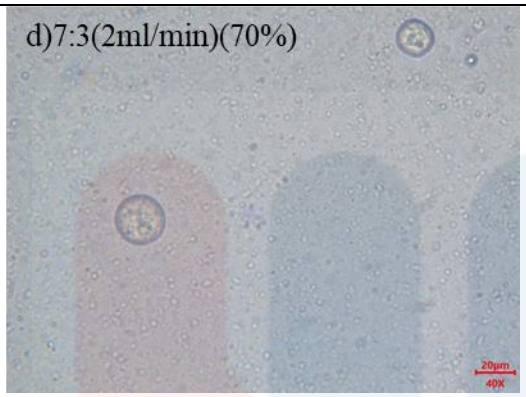
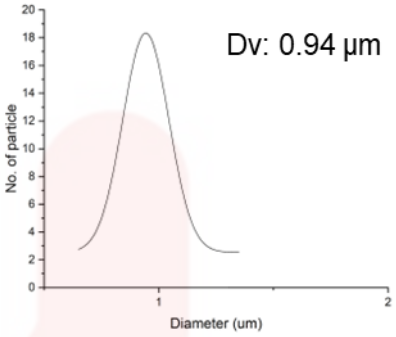
7:3		

Figure 4.1: Effect of w/o ratio for (a) 1:9, (b) 3:7, (c) 5:5 and (d) 7:3 to the size of microparticle from the optical microscope

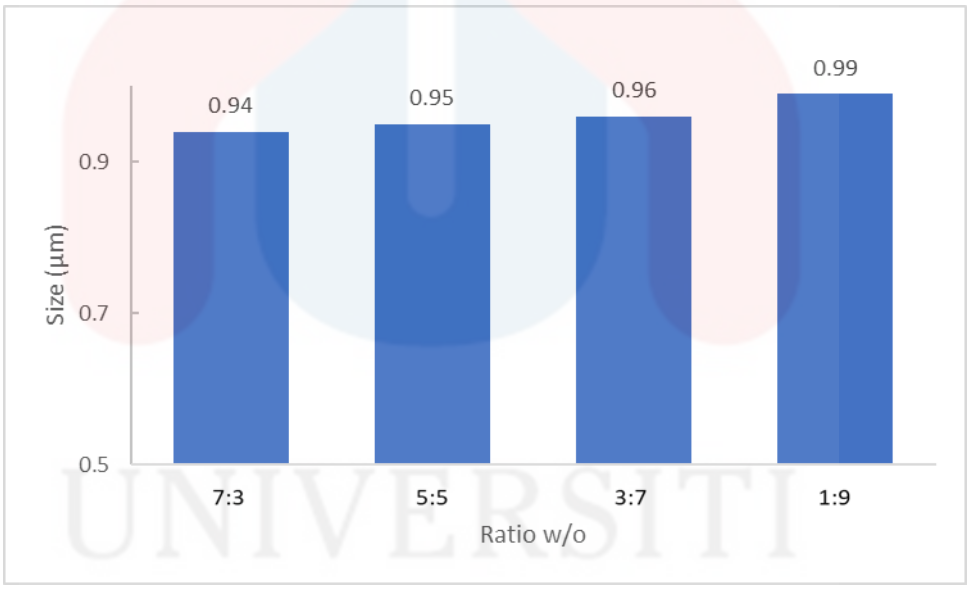


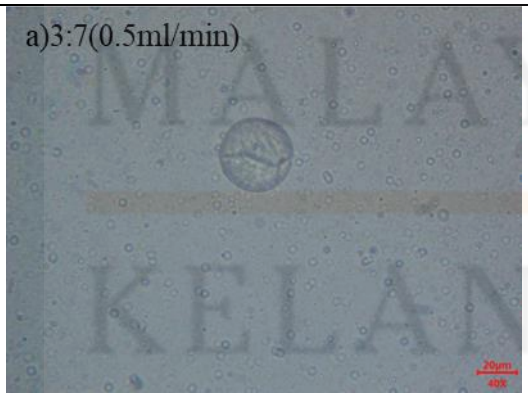
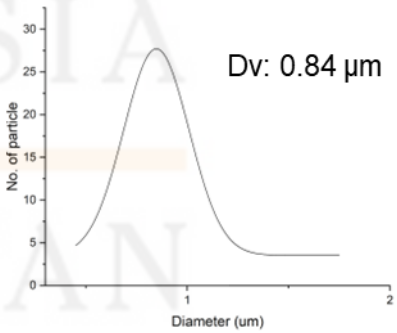
Figure 4.2: Size for PCL microparticles that impressed from different w/o ratios.

The graph showed that at a ratio of 7:3, the smaller diameter was 0.94 µm, while it continued to increase to 0.99 µm at a ratio of 1:9, which was the largest diameter. For the size distribution, the graph 1:9 is more tapered compared to the 3:7. This means that the 1:9 ratio is more homogeneous than the 3:7 ratio, the standard deviation is 0.24. This occurred because of the increase in the amount of surfactant used in the emulsion, where at a ratio of 1:9, the surfactant used was as much as 10ml, while for a ratio of

7:3, the surfactant used was 70ml. This showed that the more surfactant was used, the smaller microparticles were formed. The use of PVA as a surfactant in this experiment can be attributed to the rise in PCL microparticle size. This statement is supported by previous research, which showed that surfactants such as PVA played an important role in the formation of microparticles. The main role of surfactants was to inhibit the intermediate re-coalescence of recently produced droplets, resulting in the production of smoother, smaller microparticle surfaces (Bile et al., 2015). Other previous research also mentioned that one of the most widely used and widely accessible polymer stabilizers on the market was polyvinyl alcohol (PVA) (Kitayama et al., 2023). Because of these characteristics, PVA was a suitable stabilizer for the synthesis of microparticles for use in pharmaceutical and medical applications. A crucial factor in liquid-liquid dispersion was the presence of an appropriate stabilizer (Iqbal et al., 2015).

4.3 Effect of feeding rate to the size of microparticle

Figure 4.3 shows that the size of microparticles increased when the feeding rate was increased. Results obtained also showed similar trends as those obtained from a previous study.

Feeding rate	Microparticles of PCL (40x magnification)	Graph for size distribution of microparticles of PCL
0.5 ml/min		

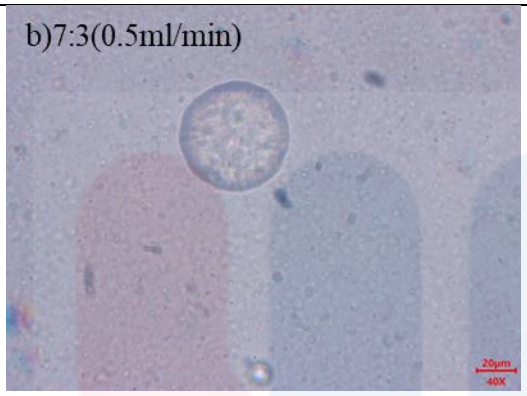
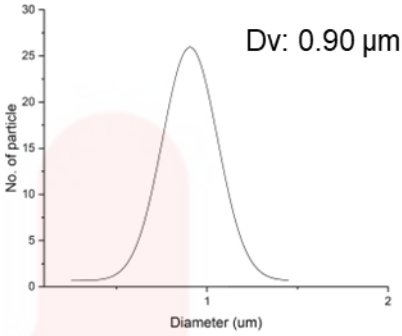
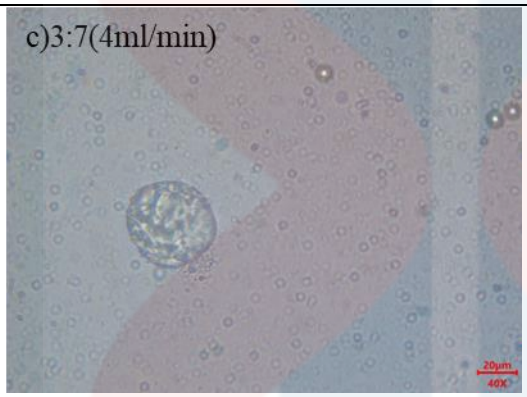
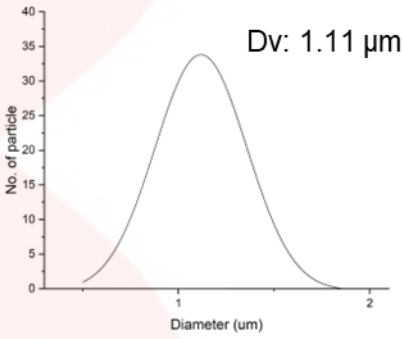
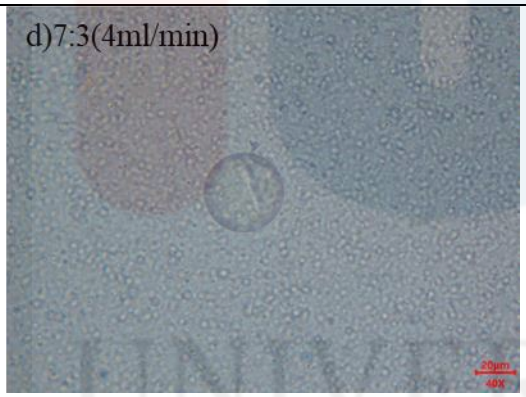
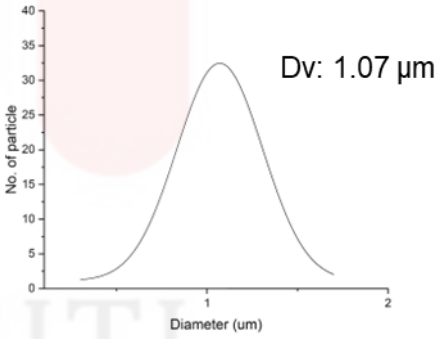
0.5 ml/min		
4 ml/min		
4 ml/min		

Figure 4.3: Effect of feeding rate for (a) 3:7 (0.5ml/min), (b) 7:3 (0.5ml/min), (c) 3:7 (4ml/min) and (d) 7:3 (4ml/min) to the size of microparticle from the optical microscope

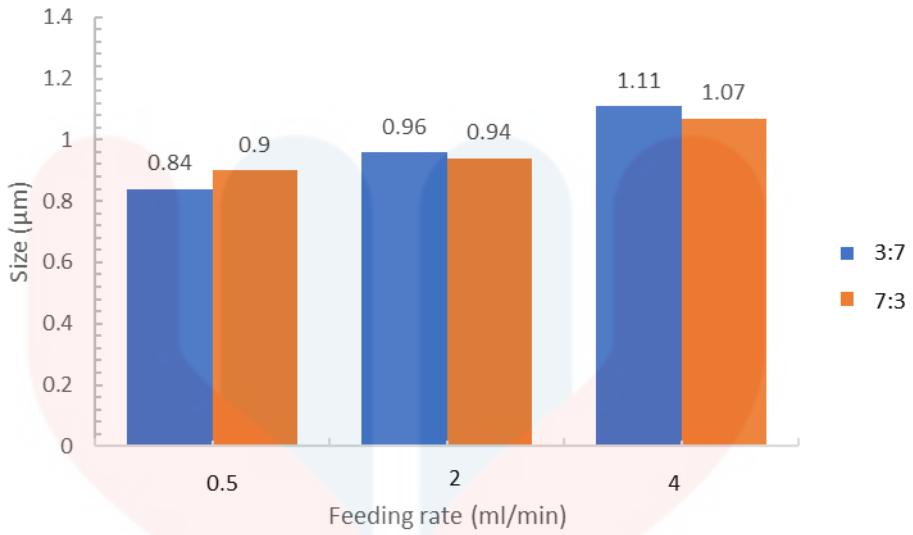


Figure 4.4: Size for PCL microparticles that impressed from different feeding rate.

The Figure 4.4 showes the microparticle size by using the difference in feeding rate. At a ratio of 3:7, the smaller size was 0.84 µm, which used a feeding rate of 0.5 ml/min, while the largest size was 1.11 µm, which used a feeding rate of 4 ml/min. At the 7:3 ratio, the smaller size was 0.90 µm, which used a feeding rate of 0.5 ml/min, while the largest size was 1.07 µm, which used a feeding rate of 4 ml/min. This happens because the droplets that fall in the oil phase using syringe pump have a lot of space to form particles. This point was also approved by previous research. The dispersed droplets were the primary site of emulsion; as the amount of water droplets converted to larger particles, more space was taken up by the particles (Bao et al., 2004).

At a feeding rate of 0.5 ml/min, it took a long time for all the water phase droplets to fall into the oil phase, while at a feeding rate of 4 ml/min, it did not take a long time for all the water phase droplets to fall into the oil phase. This was also acknowledged by previous research. Short feeding times were found to create larger particle sizes with a greater solid content (Budianto, 2008).

4.4 Effect of amplitude to the size of microparticle

The Figure 4.5, 4.6 and 4.7 shows that the size of microparticles decreased when the amplitude of the ultrasonicator was increased. Results obtained also showed similar trends as those obtained from a previous study. The graph in Figure 4.8 shows the microparticle size by using the difference in amplitude. At the 3:7 ratio, the largest size was 1.04 µm at 55% amplitude, while the smaller was 0.94 µm at 85% amplitude. At a ratio of 5:5, the largest size was 1.05 µm at 55% amplitude, while the smaller was 0.92 µm at 85% amplitude. At the 7:3 ratio, the largest size was 0.98 µm at 55% amplitude, while the smaller size was 0.79 µm at 85% amplitude. For the size distribution, at the highest amplitude of 85%, the graph of 5:5 ratio is more tapered than the amplitude at 70%. This means that higher amplitudes appear more homogeneous than lower amplitudes, the standard deviation is 0.27. At the 7:3 ratio, which is at amplitude of 70%, the graph looks more tapered than at 55% amplitude. This means that at a ratio of 7:3, at an amplitude of 70% it looks more homogeneous than at an amplitude of 55%, the standard deviation is 0.16. An increased amplitude of the ultrasonicator probe resulted in smaller microparticles, as the graph below shows.

This trend indicated that the mean size of the dispersion decreased as the ultrasonic homogenizer's amplitude increased. This was most likely caused by the system's high amplitude high-energy dissipation, which caused deformation and the breaking up of large droplets into smaller ones (Iqbal et al., 2015). It was because of a decrease in the number of cavitation bubbles that the intensity of cavitation decreased at lower ultrasonic power levels (Toraman, 2017).

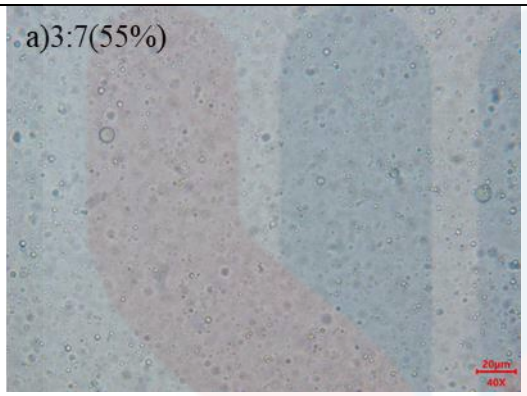
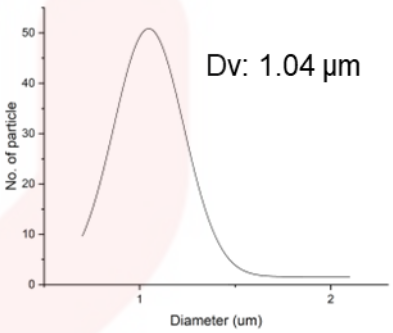
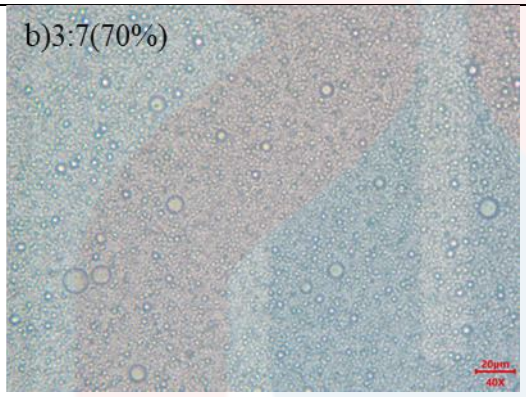
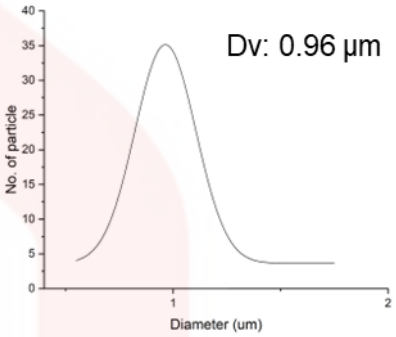
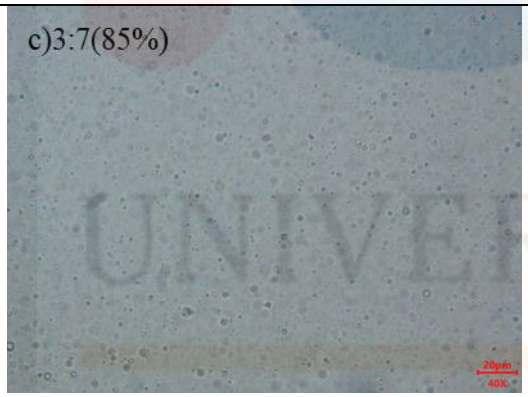
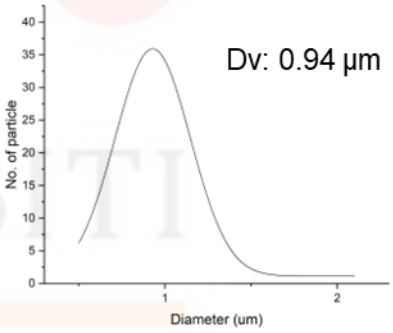
Amplitude (%)	Microparticles of PCL (40x magnification)	Graph for size distribution of microparticles of PCL
55		
70		
85		

Figure 4.5: Effect of different amplitude for (a) 3:7(55%), (b) 3:7(70%) and (c) 3:7(85%) to the size of microparticle from the optical microscope

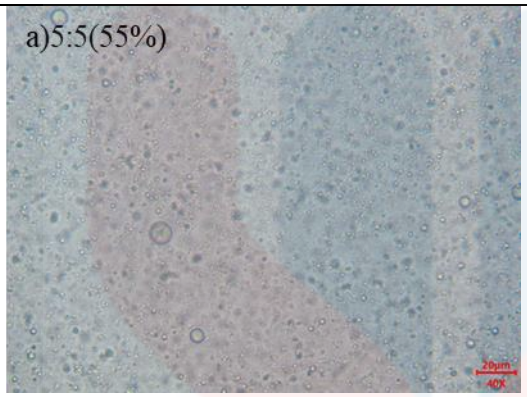
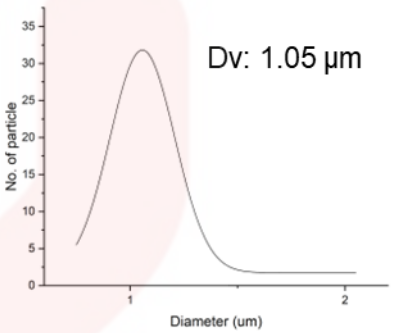
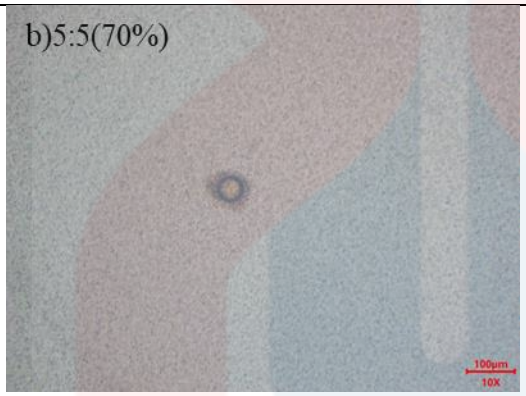
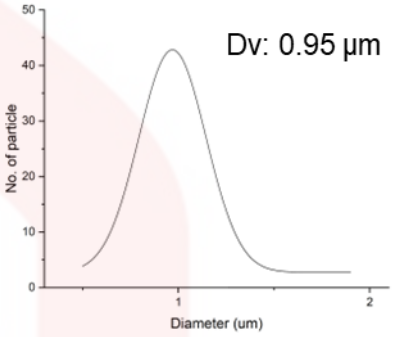
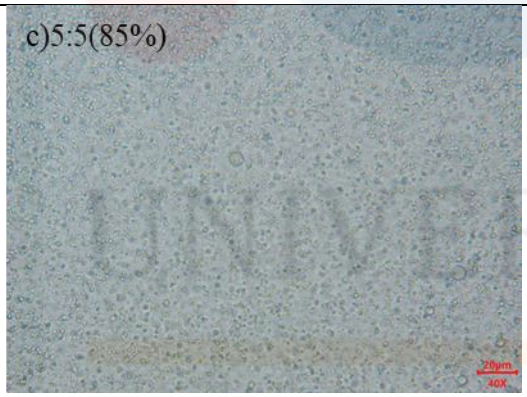
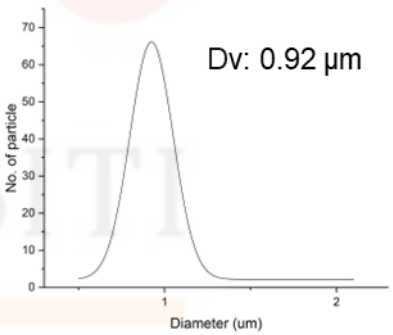
Amplitude (%)	Microparticles of PCL (40x magnification)	Graph for size distribution of microparticles of PCL
55		
70		
85		

Figure 4.6: Effect of different amplitude for (a) 5:5(55%), (b) 5:5(70%) and (c) 5:5(85%) to the size of microparticle from the optical microscope

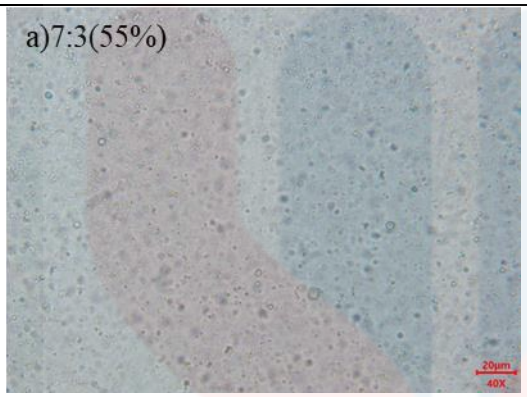
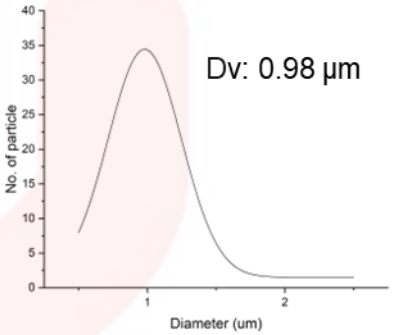
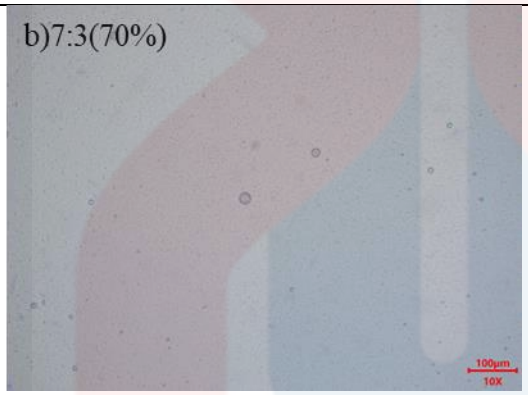
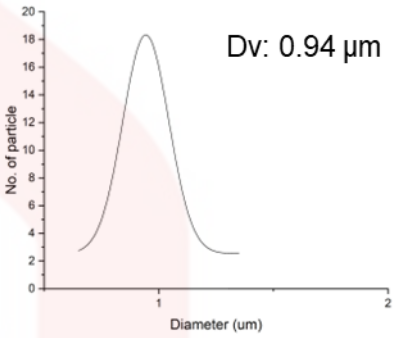
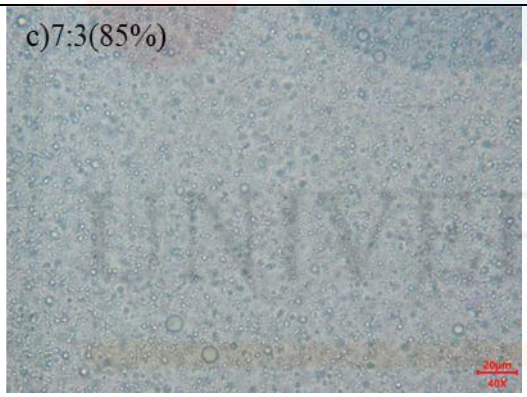
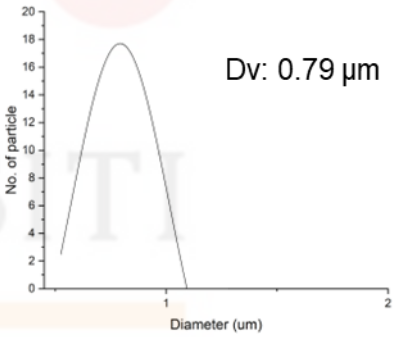
Amplitude (%)	Microparticles of PCL (40x magnification)	Graph for size distribution of microparticles of PCL
55		
70		
85		

Figure 4.7: Effect of different amplitude for (a) 7:3(55%), (b) 7:3(70%) and (c) 7:3(85%) to the size of microparticle from the optical microscope

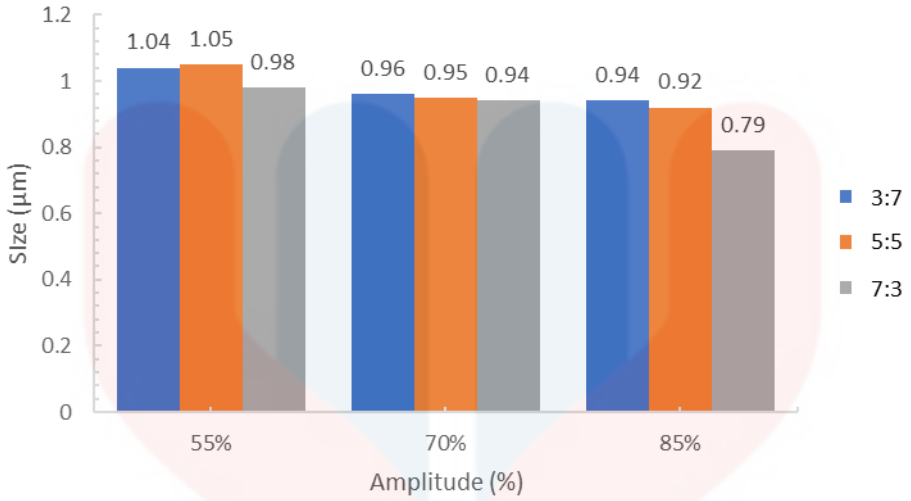


Figure 4.8: Size for PCL microparticles that impressed from different amplitude

4.5 Effect of molecular weight of PCL to the size of microparticle

From figure 4.9, it is shown that the difference between the molecular weights of PCL has been used.

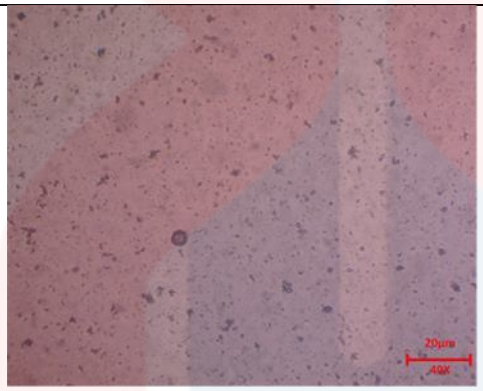
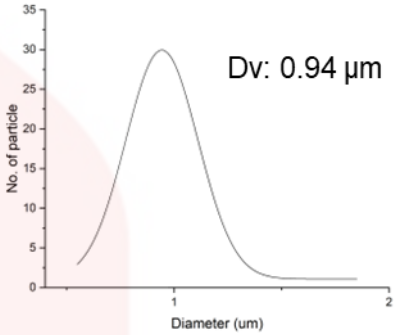
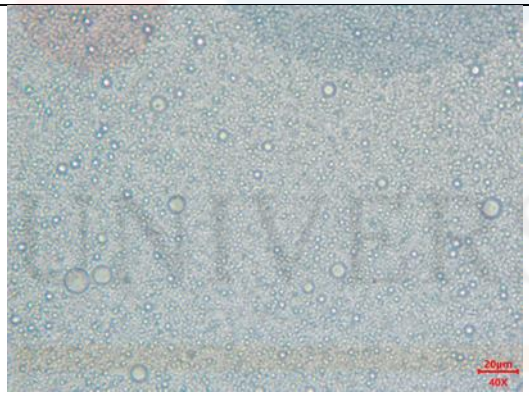
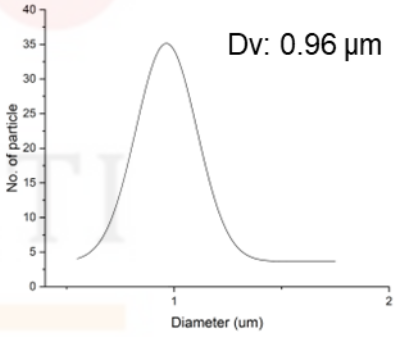
Molecular weight of PCL (kg/mol)	Microparticles of PCL (40x magnification)	Graph for size distribution of microparticles of PCL
45000		
80000		

Figure 4.9: Image effect of molecular weight of PCL to the size of microparticle from the optical microscope

The Figure 4.9 shows that a molecular weight of 80,000 kg/mol of PCL had a bigger particle size than one with a molecular weight of 45,000 kg/mol of PCL.

Previous studies have proven that higher molecular weights can produce a larger particle size. The size of the particles increased as PCL's molecular weight increased. But changes in particle size brought on by molecular weight were less than that caused by the concentration of polymers (Jeong et al., 2003).

While the size of the microparticles increased somewhat when using 80,000 kg/mol of PCL, there was only a small difference between the stability of the size of emulsion microparticles compared to 14,000 kg/mol of PCL. Due to the same amounts of PCL for both molecular weights, this might have been explained by the necessary amounts of surfactant and solvent and hollow particles also seem to form more (Jeong et al., 2003).

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

In this study, different sizes of PCL microparticles were successfully obtained using the solvent evaporation method using ultrasonicator probe with different parameters, which were water-oil ratio, feeding rate, amplitude, and molecular weight of PCL. The conclusions that were made for this study were divided into two parts: chemical parameters and physical parameters. Chemical parameters showed the smaller size microparticle in this study is 0.79µm, 7:3 w/o ratio at amplitude of 85%. Applications that can be used for small sizes are such as Drug Delivery Systems and Tissue Enginnering Scaffolds. The largest size microparticle in this study is 1.11µm, 3:7 w/o ratio with a feeding rate of 4ml/min at amplitude 70%. Applications that can be used for large sizes are such as tissue filler in cosmetic surgery and sustained drug release. Next, for the physical parameter, which is the amplitude of the ultrasonicator probe, to reduce the increasing of solution temperature during the emulsification process, 20 minutes of emulsification process with 70% amplitude where the pulse is 5 seconds run and 5 seconds stop is the most optimum to prevent heat build-up during the emulsification process. Hence, smaller, uniform-sized microparticles could be obtained.

5.2 Recommendations

This study provided comprehensive support for the utilization of the solvent evaporation method assisted by an ultrasonicator probe to generate microparticles of various sizes. This approach was well-suited for investigating the impact of parameters on microparticle size. However, it was not advisable for industrial manufacturing due to the heightened sensitivity of the environment during the emulsification process using an ultrasonicator probe. Additionally, in the evaporation process, numerous factors had to be considered to regulate the evaporation rate.

The suggestion for the future where it is possible to get hollow particles from solid to hollow is that future research could have examined at a ratio of 7:3 with a feeding rate of 2ml/min but needs to be improved on parameters such as being able to use a different concentration of polymer to get more hollow particle. The suggest for The parameter of different PVA surfactant concentrations could have been added to this investigation. To better understand the size of the particles generated, future research could also have examined PVA surfactant at a concentration of 1 wt% and 2 wt%, as it was evaluated at 0.5 wt% in this study.

Therefore, to improve the image of the size and morphology of PCL microparticles for future research, a field emission scanning electron microscope could have been used. Furthermore, the behaviour of release caused by variations in the size and morphology of PCL microparticles was also proposed to gain further insight into the application that could be made when various parameters are used.

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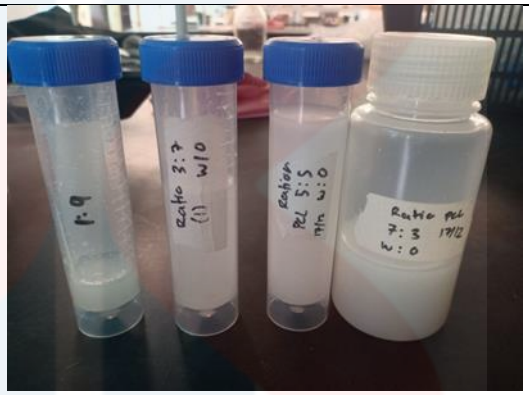
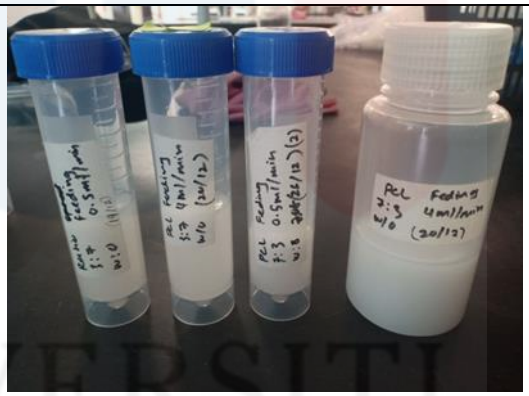
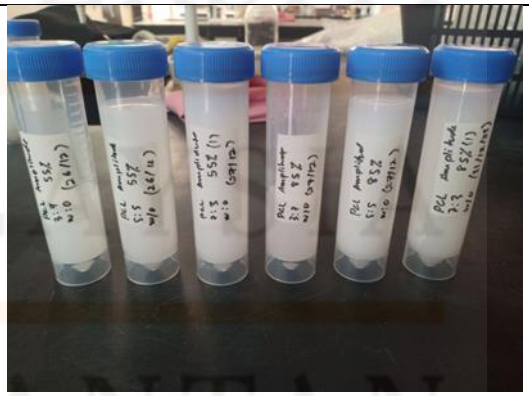
APPENDIX

Parameter	Sample
w/o ratio	
Feeding rate	
Amplitude	

Molecular weight (45,000)	

	
Water phase injected to oil phase and ultrasonicator together	Solution after ultrasonicator process
	
Solvent evaporation process	Final result after solvent evaporation