**An-Najah National University**

**Faculty of Graduate Studies**

# Biodegradable Poly (dl-lactide-co-glycolide) Microcapsules as a Drug Delivery System

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# Dedication

To: my mother, my father, my sisters,

brothers and to all of my friends and persons who have supported

me and encouraged me in this work.

# Acknowledgement

First and foremost, I am grateful to Allah Almighty who supported me to complete this thesis successfully; praise and thanks are due to Allah.

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Finally, thanks are due to my family and my friends who supported me and encouraged me.

# الاقرار

**أنا الموقع أدناه مقدم الرسالة التي تحت عنوان:**

## Biodegradable Poly (dl-lactide-co-glycolide) Microcapsules as a Drug Delivery System

اقر بان ما اشتملت عليه هذه الرسالة انما هي من نتاج جهدي الخاص باستثناء ما تمت الاشارة اليه حيثما ورد ، وان هذه الرسالة ككل ، او اي جزء منها لم يقدم لنيل اية درجة علمية او بحثية لدى اية مؤسسة تعليمية او بحثية اخرى .

## Declaration

The work provided in this thesis, unless otherwise referenced, is my own research work and has not been submitted elsewhere for any other degree or qualification.

**Student's name:** **اسم الطالب:**

**Signature:** **التوقيع:**

**Date:** **التاريخ:**

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# Lists of Abbreviation

| Symbol | Abbreviation |
|---|---|
| **PLG** | Poly (dl- lactide co-glycolide) |
| **DCM** | Dichloromethane |
| **SDS** | Sodium Dodecyl Sulfate |
| **$T_g$** | Glass Transition Temperature |
| **SEM** | Scanning Electron Microscope |
| **DSC** | Differential Scanning Calorimetry |
| **UV-vis** | Ultraviolet-Visible Spectroscopy |
| **$N_i$** | Number of PLG Microcapsules |
| **$D_i$** | Diameter of PLG Microcapsules |
| **T** | Temperature |
| **$^oC$** | Degrees Celsius |
| **C** | Concentration |
| **PVA** | Poly (vinyl alcohol) |
| **A** | Absorbance |
| **DDS** | Drug Delivery System |
| **RPM** | Revolutions Per Minute |

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## Abstract

Poly dl-lactide co-glycolide (PLG) is a biodegradable polymer that has a slow degradation rate and high permeability to small drug molecules.

PLG microcapsules were prepared by emulsifying a polymer solution that consists of PLG/solvent (dichloromethane) into a continuous phase that consists of a nonsolvent solution (water and SDS as a surfactant). After emulsification, the solvent diffuses out of polymer droplets (liquid microcapsules) to the nonsolvent solution and then evaporates at the surface of the nonsolvent to the air. The encapsulation of the limonene within the polymer microcapsules was prepared, and limonene release was determined with time from polymer microcapsules prepared.

The current study aims at studying the effect of the type of the nonsolvnet on the drug release behavior (i.e. kinetics) out of the microcapsules in relation with the properties of the polymer shell.

The drug release from the solid microcapsules was measured using spectroscopic techniques. The size of microcapsules was analyzed by optical light microscope.

The PLG microcapsules were prepared by emulsifying the polymer solution in continuous phase. The two phases were mixed for at least 2 hr

using a magnetic stirrer; the size of prepared microcapsules was measured by the light microscope.

The PLG microcapsules were prepared using different concentrations of SDS solution, methanol, and ethanol and study of its impact on the size of the PLG microcapsules.

Our results show that as the concentration of nonsolvent increases in the process of preparing of PLG microcapsules the size of prepared microcapsules decreases and the limonene release increases from polymer microcapsules with decreasing the size of microcapsules.

These results can be explained as follows: with increasing the concentration of methanol, ethanol or SDS, the viscosity of the nonsolvent increases and the interfacial tension decreases. This lead to a decrease in size of obtained PLG microcapsules and smaller microcapsules are obtained.

# CHAPTER 1

# Introduction

## 1.1 Background

Polymers are substances that have high molar masses, and consist of a large number of repeating units that are called monomer residues held together by covalent bonds [1]. There are different kinds of polymers such as synthetic polymers as polystyrene and natural biopolymers as DNA and proteins [1].

Biodegradable polymers are polymers that bio-degrade in the body by chemical reactions or by stimulating enzymes. These polymers have become increasingly important especially in pharmaceutical applications such as implants, scaffolds for tissue engineering and microcapsules as drug delivery systems [2].

Encapsulation of drugs within polymeric microcapsules is a useful process for the protection, of bioactive materials in the microcapsules, from the external environment which improves the stability of the coated materials [3]. Several polymers were used for preparation of microcapsules such as [4]: Polylactides (PLA), polyglycolides (PGA), poly (lactide-co-glycolides) (PLG), polyanhydrides and Hyaluronic acid. The chemical structures of three of these biodegradable polymers are shown in Figure 1.1:

**(a) The structure of PLG. Where n: the number of monomers of dl-lactide, and m: The number of monomers of glycolide.**

**(b) Polyanhydrides**

**(c) Hyaluronic acid**

**Figure 1.1:** Chemical structures of some biodegradable polymers (a) Poly dl lactide co glycolide (b) Polyanhydrides (c) Hyaluronic acid [5, 16].

In the last year, there was an increased interest in polymer microcapsules as a drug delivery system because it is used in many applications in life such as controlled drug release, protects the drug from the environment and improves the process of giving the drug to the patient's body [10].

There are many types of drug delivery system (DDS) such as targeted drug delivery system, which is a way to give the medication to the body by a

way that increases the concentration of the drug in a certain part of the body [6].

Thin film DDS which uses dissolving thin film of the drug that is absorbed by mouth [7], self-microemulsifying DDS that uses microemulsion that containing the solubilized drug [8], and polymer microcapsule DDS that uses polymer to form microcapsules.

Polymers to be used for controlled drug delivery should be chemically inert, nontoxic and biodegradable.

The most important factors responsible for the drug delivery rate from polymeric microcapsules are: The chemical and physical properties of drugs, the size of the particles of microcapsules, the type of polymer used in the manufacture of the microcapsules, the size of polymer microcapsules, molecular weight of polymer and the co-monomer ratio. Upon increasing the amount of the more quickly degrading monomer, the release rate increases [5, 9].

## 1.2 Polymeric Microcapsules

Microcapsule is a tiny sphere with a uniform shell surrounding it and it has a diameter of micrometer order [10].

### 1.2.1 Preparation of Microcapsules

Of the most important ways to prepare polymeric microcapsules are emulsion solvent evaporation and phase separation, which is considered one of the most important ways to prepare polymeric microcapsules [2].

In emulsion solvent evaporation method, the capsules are prepared by emulsifying a polymer solution consisting of polymer/solvent/poor solvent (i.e. oil) into a continuous phase that consists of nonsolvent solution and a proper surfactant and mixed to obtain uniform particles of microcapsules.

After emulsification, the solvent diffuses out of polymer droplets (liquid microcapsules) to the nonsolvent solution and then evaporates at the surface of the nonsolvent to the air. With elapse of time, the concentration of the solvent in microcapsules will decrease and the concentration of polymer and oil become higher and higher, since the oil is not volatile and poorly miscible with the polymer, phase separation will take place in the microcapsules. In this case, the oil will form a droplet inside the original droplet whereas the polymer will form a solid shell around the oil droplet. Solidification of the polymer occurs by glassification or crystallization [5, 9].

There are other methods for preparation of polymer microcapsules such as phase separation method. This method is dependent on phase seperation of the polymer by adding an organic nonsolvent such as (silicon oil), drugs dissolved in a polymer solution to form a mixture solution, an organic

nonsolvent is added add to the mixture, and under stirring, the polymer solvent is removed and polymer microcapsules (containing a drug) are obtained [5].

Another method for preparation of polymer microcapsules is spray drying. In this method the polymer solution is prepared by dissolving the polymer in solvent such as DCM, the drug is dissolved in polymer solution, and the mixture is sprayed through heated stream of air to obtain polymer microcapsules [5].

Interfacial polymerization is another method for preparation of polymeric microcapsules. In this method two monomers such as (diacid chloride and diamine) is used to prepare polymer microcapsules.

These monomers or other reactive monomers are dissolved in solvents to form a mixture of (oil/water) emulsion, where diacid chloride “in oil phase” and diamine “in water phase”, the monomers diffuse on to interface then react to form polymeric microcapsules shell and form polymer microcapsules [11].

### 1.2.2 Application: of Polymer Microcapsules

Polymer microcapsules are used for encapsulation of drugs and controlled drug release [12].

There are many other applications for polymer microcapsules such as agriculture especially in the area of crop protection from insects, in this

application pheromones which are insecticides are encapsulated in polymer microcapsules such as polyurea which protects it from oxidation and light, then phermones are delivered to plants by spraying the capsules containing it [13, 48, 49].

Food industry is another application for polymer microcapsules; there are some ingredients that are added to food to increase the nutritional value such as vitamins. But these ingredients may undergo oxidation or they may react with components of food, which affects the properties of food such as taste and smell. To overcome these proplems, the encapsulation of ingredients by polymer microcapsules was used to keep food and ingredients intact [13, 50, 51].

For energy generation. In this application, the deuterium (a fusion fuel) is encapsulated in a polystyrene polymer microcapsules to produce energy. The laser beam is absorbed by the surface shell of polymer microcapsules then the deuterium heats and compressing in the center of capsules resulting in fusion of deuterium nuclei to give helium, tritium and other particles that release energy [13, 52].

Some catalysts are toxic and hazardous, so acatalyst is encapsulated in polymer microcapsules to prevent danger and to facilitate its use [13, 53, 54].

The other application is to protect some materials from damage [13].

## 1.3 Microencapsulation

Microencapsulation is a method in which tiny particles of liquid or solid material such as drugs are coated by polymeric shell [14].

The process microencapsulation is the same with the process of preparation of microcapsules, but the difference in the encapsulated of drug or tiny particles in preparation.

There are many benefits for encapsulation of materials such as: to protect the material in the microcapsules from the surrounding, to control the release of materials from microcapsules. Protection of the coated parts aims at protecting them from external factors such as heat, light and humidity, and also works to control the encapsulated drugs [10, 15].

In this thesis, the polymer PLG will be used for preparation of PLG microcapsules using premix emulsification method, and studying the effect of nonsolvents such as methanol and SDS solutions on the size and size distribution of PLG microcapsules.

Limonene will be used as a model drug and will be encapsulated in the PLG microcapsules. The effect of nonsolvents, such as methanol and SDS solutions on the release of limonene from PLG microcapsules, will be investigated.

## 1.4 Poly (dl- lactide- co- glycolide) PLG

Poly dl-lactide co-glycolide (PLG) is: a polyester copolymer, consisting of the DL-lactide & glycolide monomers. This polymer is very important in medicine, because it is biodegradable, non-toxic and its biocompatibility its envolved in many medical applications. PLG resembles Poly (dl- lactic- co-glycolic acid) (PLGA) which contains lactic acid and glycolic acid monomers. In addition, this copolymer has a constant rate of biodegradation [16, 17].

The co-polymer PLG prepared from poly lactide (PLA) and poly glycolide (PG) polymers, (PLA) can found in an optically active stereoregular shape (L- PLA) and also in an optically inactive racemic shape (DL- PLA). (L-PLA) has high regularity in the polymer chain structure, so it appears as semicrystalline polymer. While (DL- PLA) is an amorphous polymer because of the irregularity in the polymer chain structure, so that the co-polymer PLG that contain (DL- PLA) is an amorphous polymer. The polymer DL-lactide co-glycolide is better than L-lactide co-glycolide because it can makes more homogeneous dispersion of the drug in the polymer matrix [18].

The glass transition temperature ($T_g$) of the (D, L- lactide- co-glycolide) is above 37 $^{o}$C, so it found in nature in a glassy form [17, 18].

The $T_g$ is the temperature at which amorphous materials shift from solid to rubber-like case, and it is always less than melting temperature, ($T_m$) [19].

PLG should be stored at a temperature equal to −20 $^{o}$C; it is soluble in some materials, such as ethyl acetate, chloroform, acetone and dichloromethane [20].

### 1.4.1 Structure and Components of PLG

Different component of the co-polymer can be prepared according to ratio (Dl-lactide/glycolide).

The monomer ratios of 50/50 and 70/30 of (D, L-lactide/glycolide) are widely used in the industry of PLG. So PLG consists of the D, L-lactide and glycolide monomers in same (50:50) or different ratio (70:30) between monomers [16].

The PLG (50:50) is the most successful polymer as drug delivery system, due to its amorphous morphology [21].

Structure of D, L-lactide and glycolide is represented in Figure1.2:

(a) (b)

**Figure 1.2:** The structures of (a) D, L-lactide and (b) glycolide [16].

Poly dl lactide is aliphatic polyester, amorphous and it has high molecular weight [22, 24]. It’s produced from ring-opening polymerization of a

racemic mixture of dl-lactide. It has a glass transition temperature between 55-60 °C [23, 24]. While poly glycolide is aliphatic polyester, linear and is made in industry by polycondensation or ring-opening polymerization of glycolide. It has a glass transition temperature at 35-40 °C [24].

### 1.4.2 Synthesis of PLG

PLG is made through opening the ring of the two monomers dl-lactide and glycolide, in a process called copolymerization. This process needs a reaction time (2h) at temperature of ($175^{o}$C).

Molar mass of monomers used in the manufacturing process of copolymer has the ratios 70/30 and 50/50 (D, L-lactide/glycolide), these are the ratios used in the polymer manufacturing process and in controlled drug delivery systems [16, 25].

The copolymerization process in the manufacturing process of PLG is represented in Figure 1.3:

**Figure 1.3:** The Manufacturing Process of PLG from Lactide and Glycolide Monomers Systems [16, 25].

### 1.4.3 PLG Applications

The most important application for PLG is in food and medicine especially in the field of drug delivery, because it is completely biodegradable in the body and nontoxic [21].

The most important other uses for this polymer are in surgery, in bone tools installed and in tissue engineering [26, 27].

PLG is used for controlled release of small particles of the drug, proteins and macromolecules such as DNA and RNA [17].

### 1.4.4 Methods of Preparation of PLG Microcapsules.

There are several techniques for preparation of PLG microcapsules. One of the most important ways: emulsion solvent evaporation/extraction method, spray drying, phase separation-coacervation, interfacial deposition.

The best of these methods are emulsion solvent evaporation/extraction, because it give uniform size distribution of microcapsules [5, 28].

Emulsion solvent evaporation/extraction in which the PLG dissolved in organic solvent such as dichloromethane (DCM), then the drug is added to the PLG polymer solution. It is then followed by addition of surfactant solution such as sodium dodyl sulfate solution (SDS) or poly vinyl alcohol (PVA) solution to the polymer-solvent-drug solution. The mixture is emulsified by stirring, in which the solvent diffuses out of the polymer by evaporation process and the PLG microcapsules are obtained.

These microcapsules are centrifuged and dried to obtain microcapsules as powder of PLG [18, 29]. Emulsion solvent evaporation/extraction method is widely used for encapsulation of drug in polymer microcapsules and for delivery of small molecule drugs [11].

There are different solvents used to dissolve PLG such as dichloromethane (DCM) [30].

One of the most important features of it is that it’s a volatile liquid, has no color and is used as solvent for wide range of organic compounds.

However this is a toxic compound and causes risk to human health because this solvent can dissolve some of fatty tissues in skin, causing chemical burns to the skin [31].

Although DCM is a toxic compound, it is used as a solvent for polymers because it is very good solvent and fast deicing for some of the polymers as PLG. Moreover, in this work it will be evaporated and removed completely during emulsification of the polymer solution during preparation of microcapsules and then the microcapsules obtained will not contain DCM.

The structure of dichloromethane is presented in Figure 1.4:

**Figure 1.4:** The structure of dichloromethane.

Premix emulsification is relatively modern emulsification technique that offers better control over the size and size distribution of the microcapsules. This technique has been proposed in the literatures for preparation of uniform size distribution of polymer microcapsules [32, 33].

In the process of preparing PLG microcapsules, suitable surfactant needed which helps in the formation process of the microcapsules such as PVA or SDS.

SDS is an organic compound with molecular formula $CH_3(CH_2)_{11}OSO_3Na$ and it is anionic surfactant. SDS in the form of powder it is highly soluble in water.

It's used in many applications such as in clothing detergents and hemoglobin analysis process [34].

The structure of sodium dodecyl sulfate (SDS) is presented in Figure 1.5:

**Figure 1.5:** The structure of SDS compound [34].

In this study, SDS solution will be used as surfactant in the preparation of microcapsules of PLG.

### 1.4.5 Controlled Release for Encapsulated Drugs within PLG Microcapsules or Other Polymer Microcapsules.

PLG microcapsules are used for encapsulation of drugs, proteins, DNA, RNA macromolecules and vitamins and others [35, 57].

There are many drugs, proteins and nucleic acids which need delivery systems such as polymer microcapsules to prevent the side effect of the drug and to facilitate the submission to the patient [58, 59].

There is scientific research about microencapsulation and release of limonene from polymer microcapsules and films. Rodrigues et.al [36] used

Polyurethane−urea polymer to make microcapsules and microencapsulation of limonene oil as the active agent by using interfacial polymerization method. They studied the effect of microcapsules on textile applications. Where a textile was soaked with polymer microcapsules solution. They found that the adhesion between textile and microcapsules increases the durability of textile fibbers. Esfanjani et.al [37] used edible films that consist of edible biopolymers such as proteins, carbohydrates and lipids for encapsulation and release of active agent of foods such as limonene.

Prakash et.al [55] used cellulose polymers for preparation of microcapsules using solvent evaporation method and encapsulation of drug (lamivudine), for studying the lamivudine release from microcapsules with time, they found that all microcapsules were spherical and the release of drug from microcapsules take less than a day.

Magharla et.al [35] used poly (lactide-co-glycolide) (PLG) for encapsulation of contraceptive steroids and ethinyl estradiol and they studied the release from microcapsules, they found that the release of drug takes a few weeks to complete.

Martins et.al [56] prepared polylactide microcapsules, encapsulation within thyme oil and the release of thyme oil was studied with time. They found that the release is faster in the first hour and remains constant in the next days.

In this work we will use limonene as a drug model where it will be encapsulated in PLG microcapsules. Limonene is a colorless liquid hydrocarbon and is used in many industries, it is used in food manufacturing and medicines. (Figure 1.6) shows the structure of limonene. And it is irritating to the skin and respiratory system. It is has a molecular formula $C_{10}H_{16}$ [47].

**Figure 1.6:** The structure of limonene**.**

Controlled drug delivery has a significant positive impact on medicine and treatment. Controlled drug release that could happen by the carrier material and the active ingredients, as the carrier material consists of materials biodegradable polymers such as PLG.

Controlled drug delivery working on the medicine for the body dump regularly, reduce the side effects and provide better treatment for the body [38, 39 ].

There are a lot of factors that affect the drug release rate such as: molecular weight of polymer, polymer composition and the size of microcapsules.

The molecular mass of polymer affect the degradation and drug release rate. Increasing the molecular mass of the polymer decreases the polymer degradation and reduces the diffuse of drugs which reduces drug release rate.

The co- monomer ratio of the copolymers also affect the drug release rate, increasing the most degrading monomer content increases the drug release rate [9, 40, 46].

### 1.4.6 Degradation Process of PLG.

Degradation of PLG occurs through decomposition process of the ester bond, as the process of decomposition increases with time. In organisms such as human PLG degradation into lactic acid and glycolide acid that degrade in the body into carbon dioxide and water [21, 41].

The structure of decayed materials PLG that is lactic acid and glycolic acid is represented in Figure 1.7:

**Figure 1.7:** The structure of lactic acid and glycolic acid.

## 1.5 Aims of the Study

The main aims of this study can be summarized as:

1) Preparation of PLG microcapsules with well defiend size and size distribution using premix emulsification method.

2) Encapsulation of limonene within PLG microcapsules for controlled release study.

3) Investigating the effect of certain substances such as nonsolvent as SDS and methanol on the size and size distribution of PLG microcapsules and limonene release from PLG microcapsules.

4) Study of the effect of PLG microcapsules size on limonene release from PLG microcapsules.

# CHAPTER 2

# Experimental

## 2.1 Chemicals and Reagents

PLG that has molecular weight of 40000 – 75000, and lactide glycolide ratio of (50:50) was purchased from Sigma-Aldrich. Limonene (97%), methanol (99%), ethanol (99.85%), and sodium dodecyl sulfate (SDS) (98.5%) were supplied by Sigma-Aldrich Company and used as received unless otherwise specified. Dichloromethane (DCM) (99.98%) was purchased from Frutarom. Dipotassium hydrogen phosphate ($K_2HPO_4$) (99%) and monopotassium dihydrogen phosphate ($KH_2PO_4$) (99%) were purchased from Riedel Company.

### 2.2 Preparations of PLG Microcapsules.

In this study, premix emulsification was used to prepare the PLG microcapsules. 0.5 g of PLG was dissolved in 24.5 g DCM to prepare a 2% (wt/wt) stock solution. To 1 g of this solution, 1 g DCM and 0.25 g limonene were added. This mixture was added to 10 g of 10% (w/w) (SDS/water) solution. All ingredients were mixed for 2 h with a magnetic stirrer at approximately 1000 rpm to form PLG microcapsules. Different types of alcohols at different concentrations were added to the mixture after 1 min starting stirring (i.e. emulsification). During stirring, the DCM migrated from the polymer phase into the nonsolvent phase and evaporated to the air, leaving behind it a solid microcapsules.

These microcapsules were collected by centrifugation at 3000 rpm for 20 min, and washed with water to remove the SDS for three times.

To obtain the microcapsules as powder, the microcapsules were filtered using a filter paper. The aforementioned procedure was repeated using different nonsolvents. As indicated in Table 2.1.

**Table 2.1: Compositions of the Nonsolvent Used in the Preparation of PLG Microcapsules.**

| formualtion | SDS solution | methanol | ethanol |
|---|---|---|---|
| 1 | 11 g of 10% SDS | 0 | 0 |
| 2 | 11 g of 5% SDS | 0 | 0 |
| 3 | 11 g of 2% SDS | 0 | 0 |
| 4 | 10 g of 10% SDS | 1g | 0 |
| 5 | 9 g of 10% SDS | 2g | 0 |
| 6 | 8 g of 10% SDS | 3g | 0 |
| 7 | 9 g of 10% SDS | 0 | 2g |

The method for preparation of microcapsules is shown in Figure 2.1:

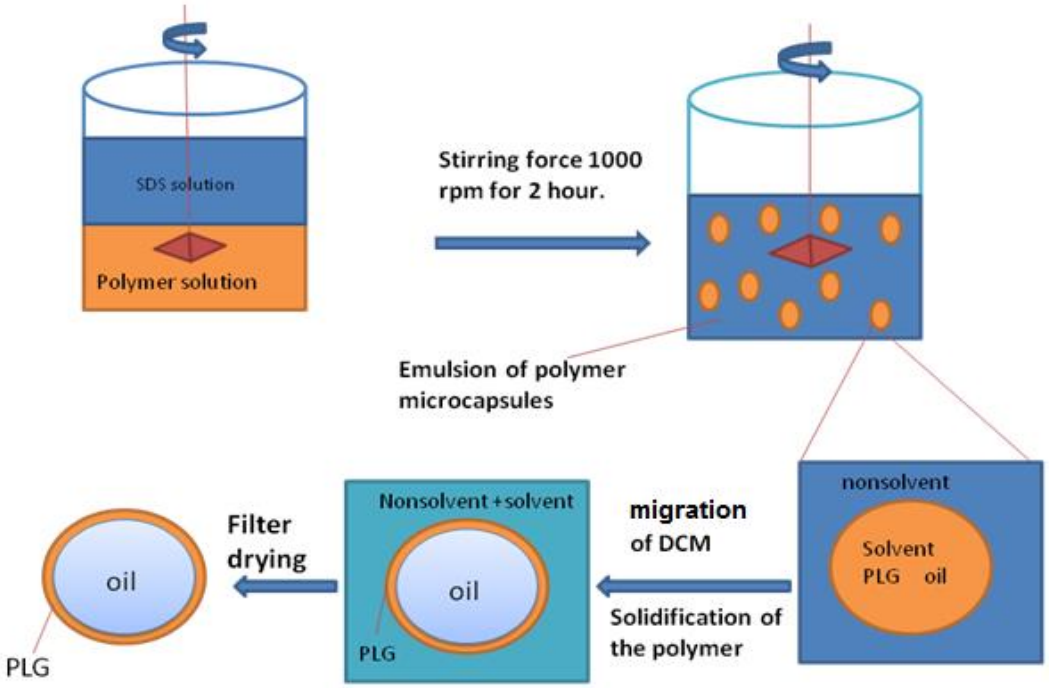



**Figure 2.1:** Preparation of PLG Microcapsules

## 2.3 Size and Size Distribution of PLG Microcapsules Measurements.

To determine the size and size distribution of microcapsules, light microscopy device (Optical, England) was used. PLG microcapsules, right after emulsification, were diluted and visualized by the microscope at 100X Magnification. The size of at least 50 microcapsules was measured and the average size was calculated using equation 1.

**Average size of microcapsules = $\Sigma N_i D_i / \Sigma N_i$.** equation 1

Where $N_{i:}$ the number of microcapsules, and $D_i$: the diameter of PLG microcapsules (µm).

## 2.4 Measurements of Limonene Release from PLG Microcapsules.

### 2.4.1 Calibration Curve Preparation.

The concentration of limonene release with time from PLG microcapsules was measured by UV-visible spectrophotometer (UV-visible spectrophotometer Shimadzu- Model No: UV-1601, double beam spectrophotometer wavelength range 190-1100 nm, accuracy ± 0.004).

The calibration curve of limonene (i.e. absorbance vs. concentration) was prepared by dissolving 0.25 g limonene with 11 g of 0.1 M potassium phosphate buffer solution with pH = 7.4. The buffer solution was prepared by mixing 80.2 mL of 1M dipotassium hydrogen phosphate ($K_2HPO_4$) with 19.8 mL of 1 M monopotassium dihydrogen phosphate ($KH_2PO_4$).

The absorbance of different concentrations of limonene in 0.1M potassium phosphate buffer was prepared by dilution with water was measured at $\lambda$ = 200 nm and the calibration curve was constructed between the absorbance and the concentrations of limonene.

### 2.4.2 Measurements of the Limonene Release.

The concentration of limonene release with time from PLG microcapsules was measured by UV-visible spectrophotometer, 10 mg of PLG microcapsules were placed into tubes that contain 11 mL release medium (potassium phosphate buffer solution with pH = 7.4), under agitation for two weeks using a shaker at 37$^{o}$C and 100 rpm. At desirable time intervals,

the microsphere suspension was centrifuged at 3000 rpm for 10 min. Certain amount of the supernatant was withdrawn and the amount of limonene released was determined by measuring absorbance in the supernatant.

## 2.5 Scanning Electron Microscopy (SEM).

The morphology of the microcapsules was observed by scanning electron microscopy (SEM) of the type (FE-SEM. JEOL JSM-6700F). The SEM images were also used to study the size of microcapsules.

# Chapter Three

# Results and Discussion

## 3.1 Effect of the SDS Concentration on the Size of PLG Microcapsules.

The PLG microcapsules were prepared by emulsifying the polymer solution into the continuous phase that consists of different SDS concentration (10% w/w of SDS in water).

Figure 3.1, shows microscopic photographs of PLG microcapsules prepared with different SDS concentration. The size of at least 50 microcapsules was measured (see the appendix) and the average size was calculated using eq.1. The effect of SDS concentration on the average size and size distribution of the PLG microcapsules is shown in Figure 3.2 (a and b).

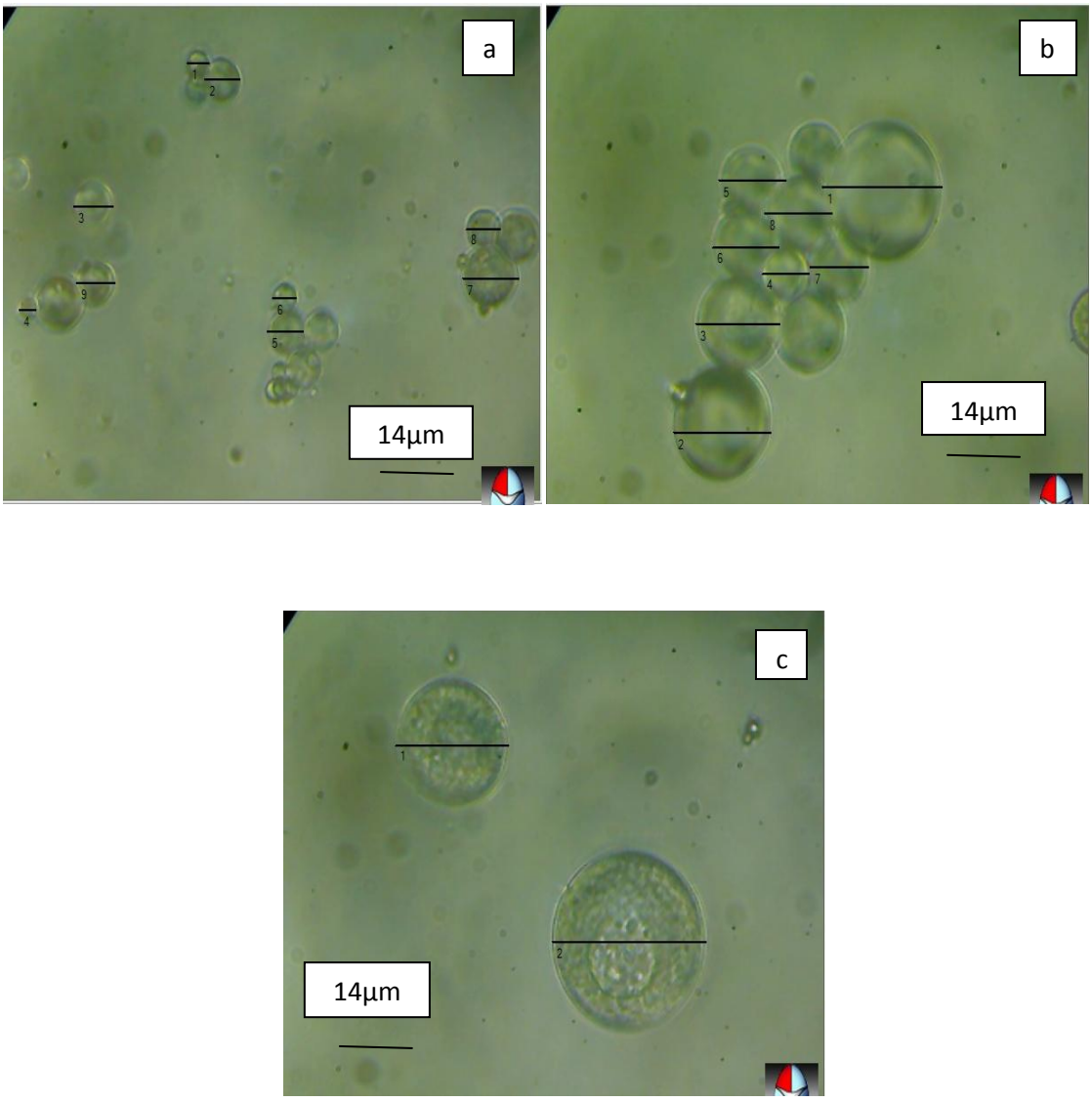



**Figure 3. 1.** The size of PLG microcapsules prepared with a) 10% (w/w) SDS solution, b) 5% (w/w) SDS solution and c) 2% (w/w) SDS solution, measured by light microscope.

Figure 3.1 (a and b ) shows when 10% SDS solution was used in the process of preparing PLG microcapsules the size of PLG microcapsules was smaller than when 5% SDS solution was used, and the size of PLG microcapsules became more bigger when 2% SDS solution was used as shown in Figure 3.1(c).

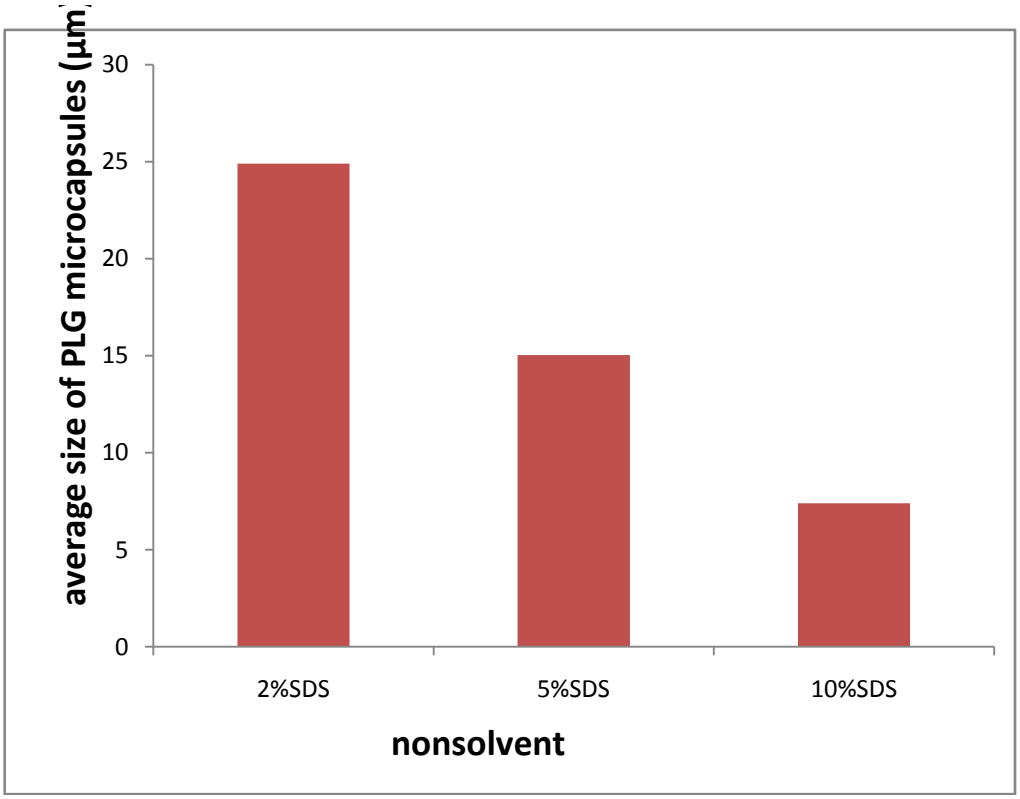



**Figure 3 .2:** (a): The average size of PLG microcapsules prepared with different concentration of SDS solution**.**

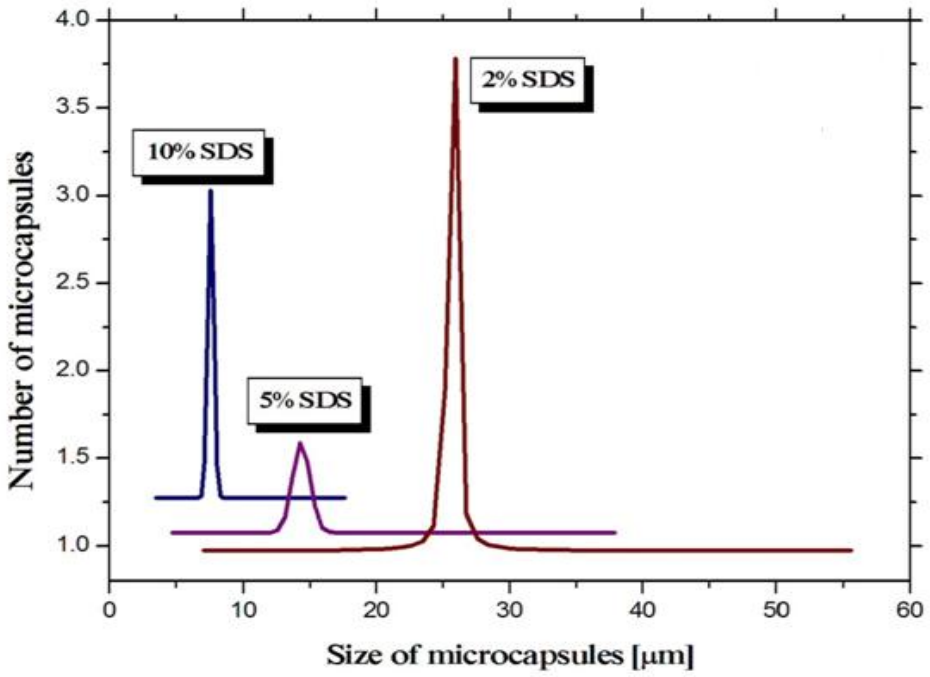



**Figure 3.2: (b):** The size distribution of PLG microcapsules prepared with different concentration of SDS solution**.**

Figure 3.1 and Figure 3.2 (a and b) shows that as the concentration of SDS solution increases the size of PLG microcapsules decreases.

For instance, when 10% w/w SDS solution was used, the average size of PLG microcapsules was 7.4 µm, with 5% SDS the average size was 15.03 µm and microcapsules, with an average size of 24.9 µm, were obtained with 2% SDS.

These results can be explained as follows: Increasing the concentration of SDS solution increases the viscosity of the continuous phase which increases the shear force applied on the droplets during emulsification, hence the size of the microcapsules consequently decreases.

In addition, the increase in the SDS concentration decreases the interfacial tension which facilitates the droplet break up resulting in small microcapsules. These results are in good agreement with the findings of other researchers [42, 43, 44].

Rong et.al [42] studied the effect of parameters such as PVA nonsolvent solution on the size distribution of polylactide microcapsules, prepared using emulsification technique, and they found that as the concentration of PVA increases the size of microcapsules prepared decreases.

Sawalha et.al [44] studied the effect of nonsolvents such as water, alcohol on the size and size distribution of microcapsules prepared using emulsification method, and they found that as the concentration of nonsolvent increases, the size of microcapsules decreases.

Brunner et.al [43] have studied the effect of PVA solution on the size of biodegradable microcapsules of poly (butylene succinate) and they found that as the concentration of PVA solution increases, the size of polymer microcapsules decreases.

The discussion above show that SDS solution is a good nonsolvent solution in the process of preparing PLG microcapsules, because it helps in controlling the size of polymer microcapsules as we needed.

## 3.2 The Effect of the Concentration of Methanol and Ethanol on the Size of PLG.

The PLG microcapsules were prepared by emulsifying the polymer solution into the continuous phase that consists of 10% SDS concentration (10% w/w of SDS in water) and certain amount of methanol or ethanol of different concentrations.

Figure 3.3, shows microscopic photographs of PLG microcapsules prepared with different methanol or ethanol concentration. The size of at least 50 microcapsules of these shown in Figure 3.4 (a and b) was measured (see the appendix) and the average size was calculated using eq. 1 page 22.The effect of methanol and ethanol concentration on the average size and size distribution of the PLG microcapsules is shown in Figure 3.4 (a and b).

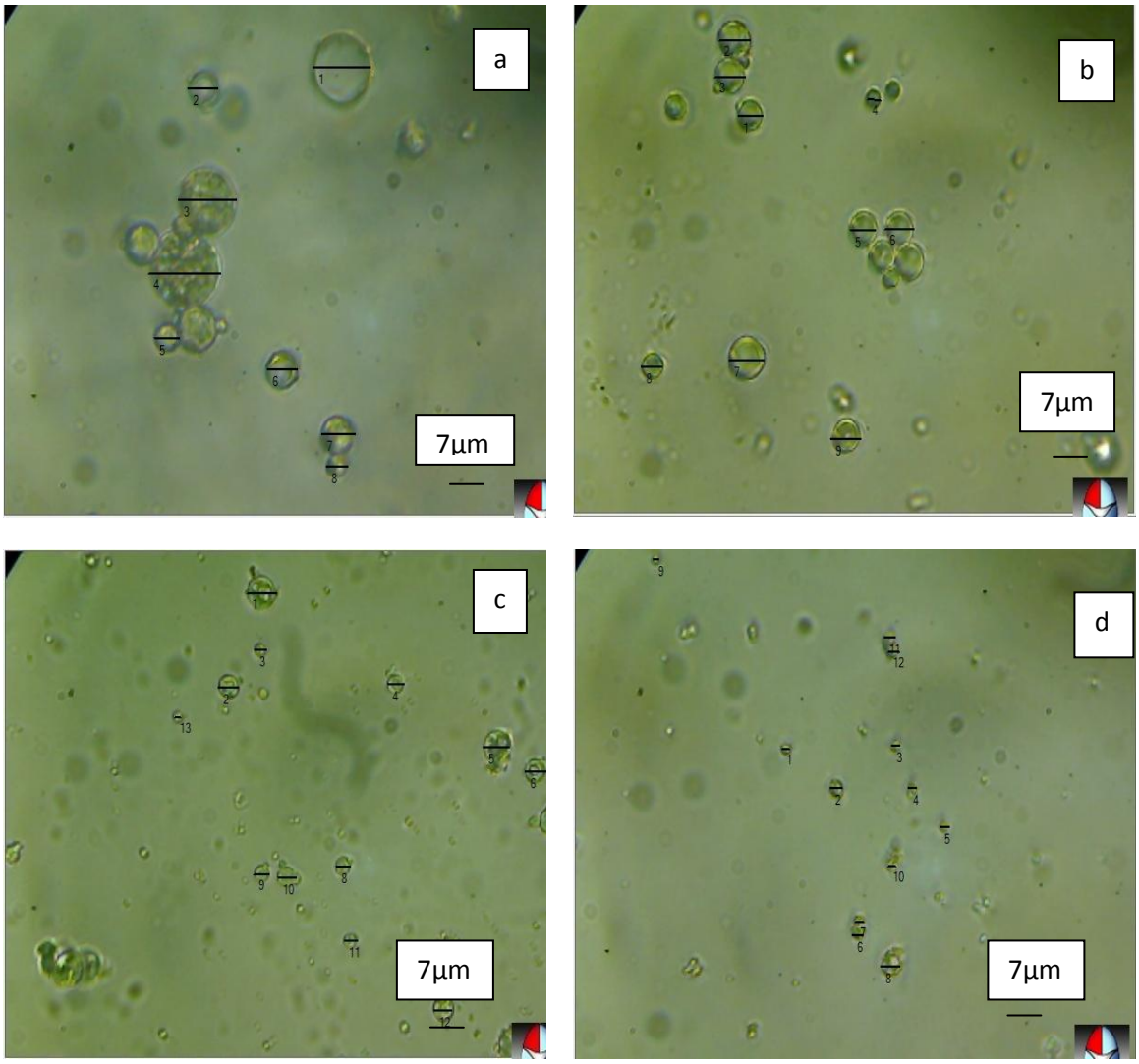



**Figure 3. 3** : The size of PLG microcapsules prepared with (10 % (w/w) SDS solution) and a) 9% methanol b) 18% methanol c) 27% methanol d) 18% ethanol, measured by light microscope.

Figure 3.3 shows when 18% methanol was used in the process of preparing PLG microcapsules, the size of microcapsules was smaller than when 9% methanol was used, and with increasing methanol to 27% the size of microcapsules became smaller than others.

This shows that as the concentration of methanol increase in the process of preparing PLG microcapsules, the size decreases.

Figure 3.3 also shows that using ethanol as nonsolvent results in smaller microcapsules in comparison with methanol at same conditions.

When 18% ethanol was used the size of PLG microcapsules became smaller than when 18% methanol was uses. This is because ethanol increases the viscosity and decreases the interfacial tension of the nonsolvent more than methanol and as the viscosity increases and interfacial tension decreases the size of microcapsules decreases [60, 44].

From discussion above show that as the concentration of alcohol increases, the size of PLG microcapsules decreases.

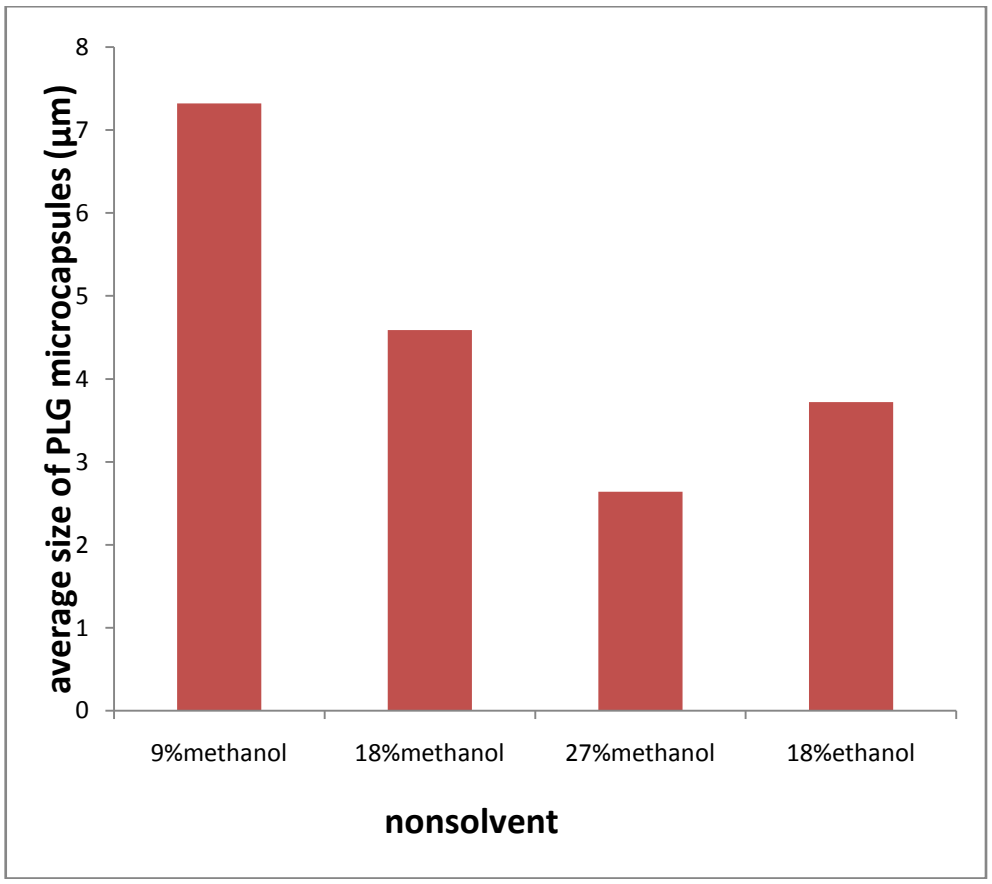



**Figure 3 .4: (a):** The average size of PLG microcapsules prepared with different concentration of methanol and ethanol.

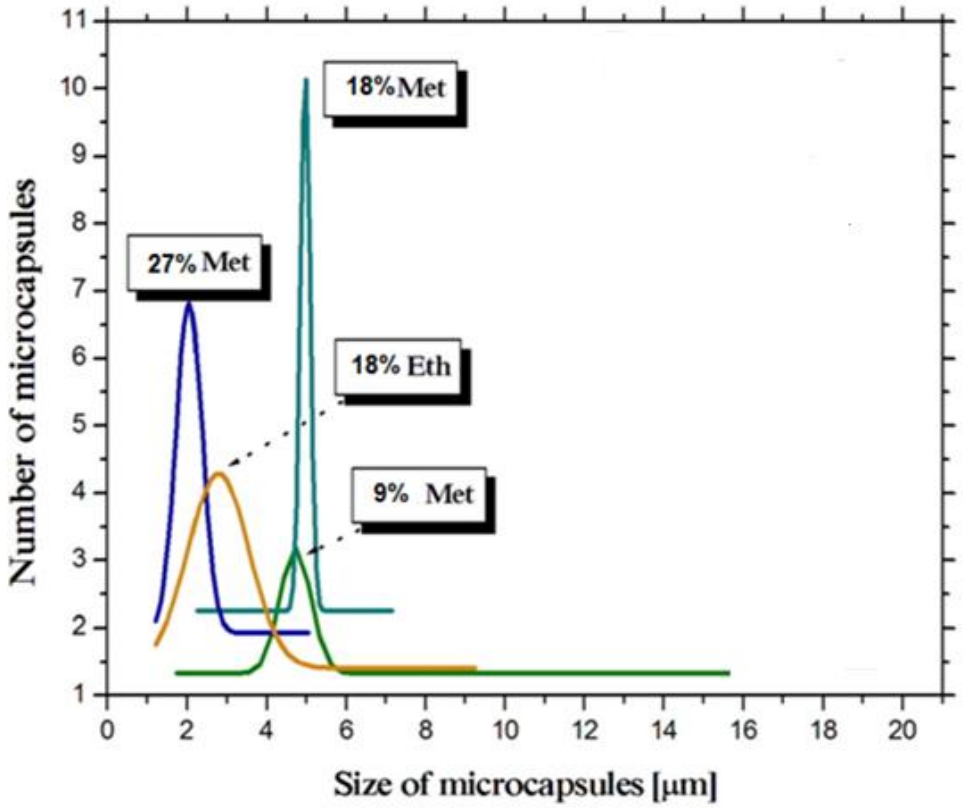



**Figure 3. 4 (b):** The size distribution of PLG microcapsules prepared with different concentration of methanol and ethanol**.**

Figure 3.3 and Figure3.4. (a and b) shows that as the concentration of alcohol solution increases, the size of PLG microcapsules decreases. For instance, when 9% w/w methanol solution was used, the average size of PLG microcapsules was 7.32 μm, with 18% methanol the average size was 4.59 μm, with 27% methanol the average size was 2.64 μm, and microcapsules with an average size of 3.72 μm were obtained with 18% ethanol.

These results can be explained as follows: increasing the concentration of alcohol solution increases the viscosity of the continuous phase and decreases the interfacial tension which facilitates the droplet break up resulting in small microcapsules; hence the size of the microcapsules

consequently decreases. This is in agreement with the findings of other researchers [44, 60].

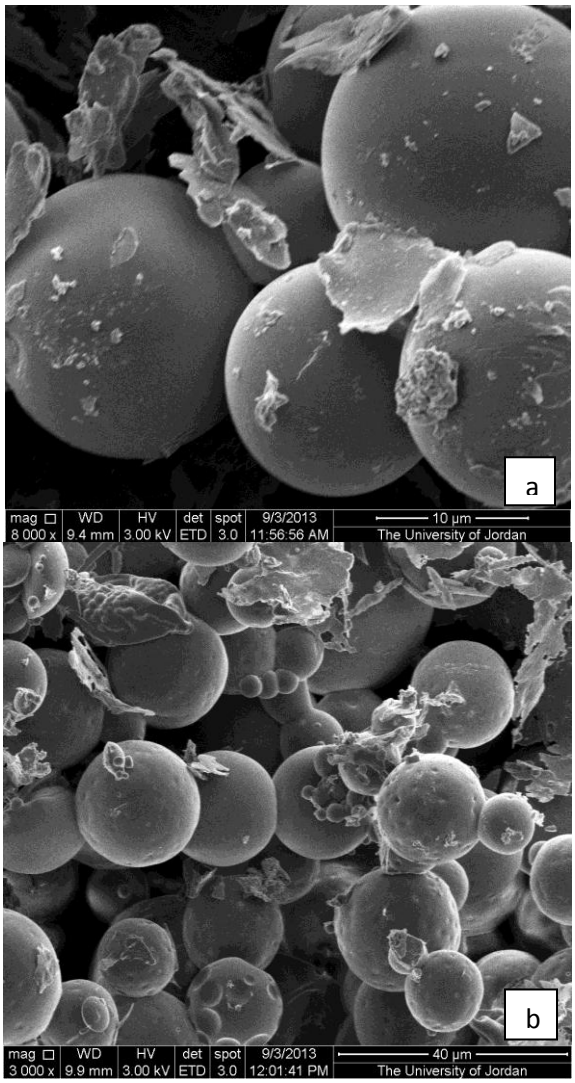
Figure 3.4(b) shows that the size of the microcapsules decreases with increasing alcohol concentration.

Sawalha et.al [44] studied the effect of methanol, ethanol and propanol in PVA nonsolvent solution on the size of polylacide microcapsules; they found that as the alcohol concentration increases the size of microcapsules decreases.

Prasertmanakit et.al [60] studied the effect of some factors such as the polymer concentration and nonsolvent as span 80 on the size of ethyl cellulose microcapsules and the release of folic acid from ethylcellulose microcapsules, they found that as the concentration of surfactant increases, the size of microcapsules decreases and the release of folic acid increases.

## 3.3 SEM results

The morphology of the PLG microcapsuels was visualized using SEM technique. Figure 3.5 shows SEM microgrpahs of microcapsules prepared with a) 10% SDS, b) 5% SDS, c) 18% methanol and d) 18% ethanol. As can be seen form the micrographs, most of the microcapsules have spherical shape and are intact.


a
mag WD HV det spot 9/3/2013 10 µm
8,000 x 9.4 mm 3.00 kV ETD 3.0 11:56:56 AM The University of Jordan
b
mag WD HV det spot 9/3/2013 40 µm
3,000 x 9.9 mm 3.00 kV ETD 3.0 12:01:41 PM The University of Jordan

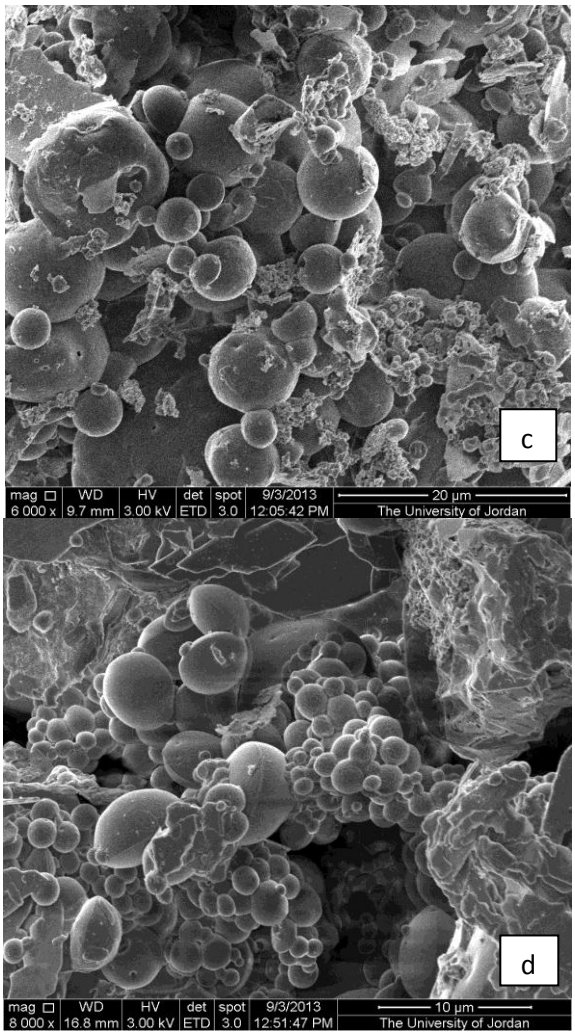



**Figure 3.5:** SEM micrographs of prepared microcapsules with a) 10% SDS, b) 5% SDS, c) 18% methanol, d) 18% ethanol.

It is quite obvious that the microcapsuels prepapred with alcohol present in the nonsolvnet are smaller in size and more uniform than those prepared by water (without alcohol) and these results obtained from light microscopy. This is because alcohol increases the viscosity and decreases the interfacial tension of the nonsolvent more than water (SDS without alcohol) and as the viscosity increases and interfacial tension decreases, the size of microcapsules decreases [44].

## 3.4 DSC Results.

A thermal property of the PLG particles, namely glass transition temperature ($T_g$), was characterized using DSC technique. Figres (3.6 – 3.10) shows DSC thermographs of PLG particles prepared with different nonsolvent compositions. The results showed that when 10% SDS solution was used, the $T_g$ for PLG microcapsules was about 75.7$^oC$, where as with 2%SDS, the $T_g$ of the microcapsules was 71.3$^0C$ (see Table 3.1).

Table (3.1) shows also that the type and concentration of alcohols in the nonsolvent affected the $T_g$ of the capsules; increasing the methanol concentration from 18% to 27% increases the $T_g$ of the capsules from ~ 74$^oC$ to 76 $^oC$. Furthermore, capsules prepared with 18% ethanol showed a higher $T_g$ (82 $^oC$) as compared to methanol (76$^oC$). The effect of the concentration and type of alcohol in the nonsolvent on the $T_g$ of the PLG microcapsules could be attributed to the different mutual interaction and the solidification rate of the microcapsules. For instance, increasing the methanol concentration increases the migration rate of DCM from the microcapsules and hence the capsules solidified faster which gets the polymer faster into the glassy state and may increase the $T_g$ of the capsules.

As the $T_g$ of the polymer increases the drug release from microcapsules decreases [45, 64].

Qiongyu et.al [45] studied the drug release from hybrid polyurethanes polymer and the effect of some factors on the release rate such as thickness

and $T_g$ of hybrid polyurethanes polymer, they found that as the $T_g$ of the polymer increases the drug release decreases.

Zhang et.al [64] studied the effect of $T_g$ of microcapsules such as poly (DL-lactide) microcapsules on drug release, they found that as the $T_g$ increases the drug release decreases.

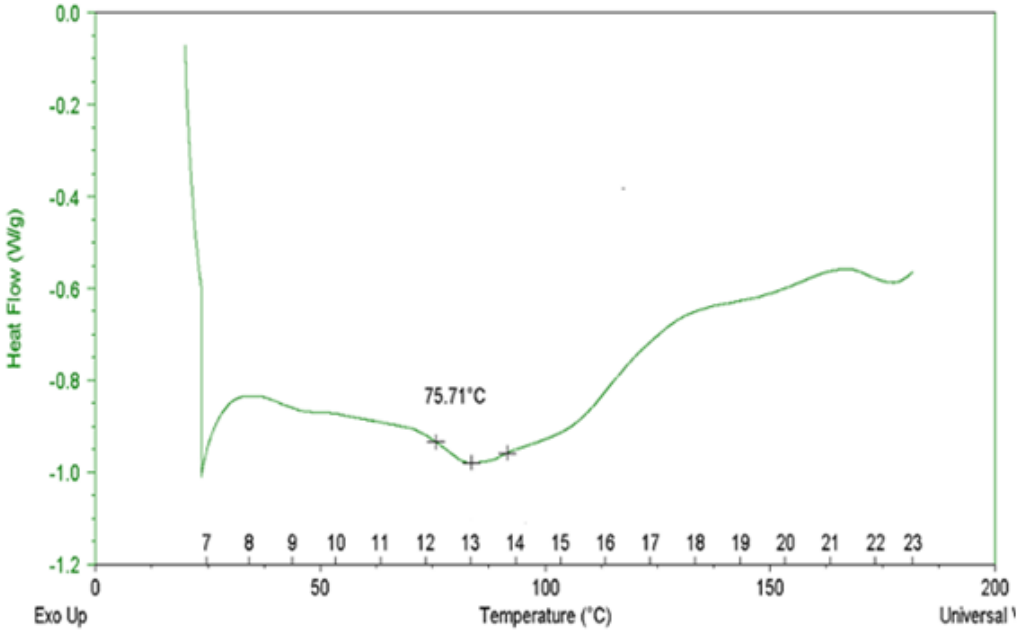



**Figure 3.6.** DSC result for PLG microcapsules prepares with 10%SDS solution**.**

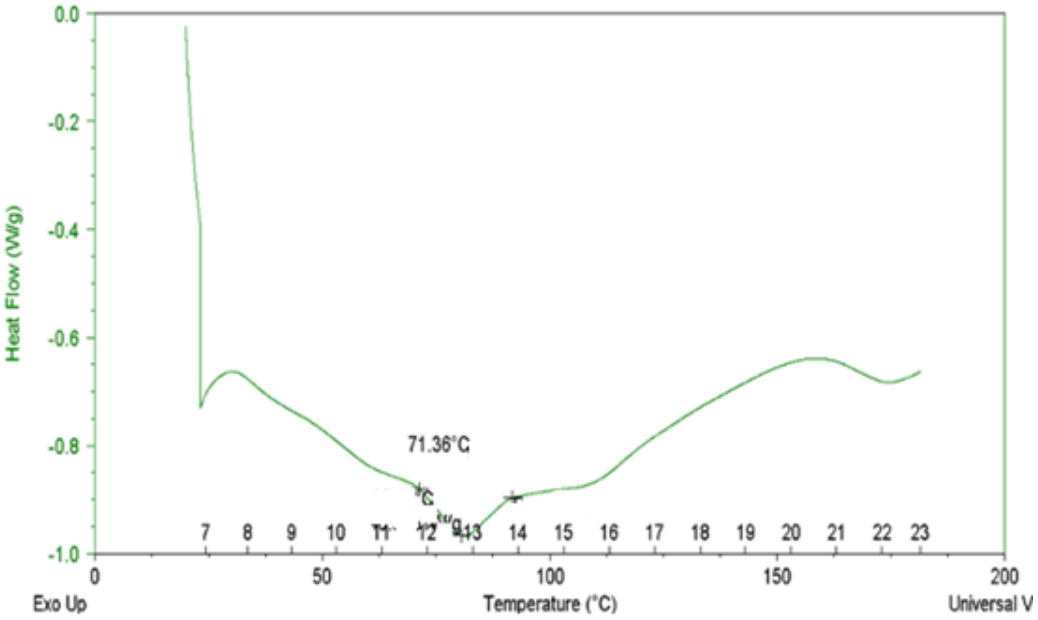



**Figure 3.7**. DSC result for PLG microcapsules prepares with 2%SDS solution.

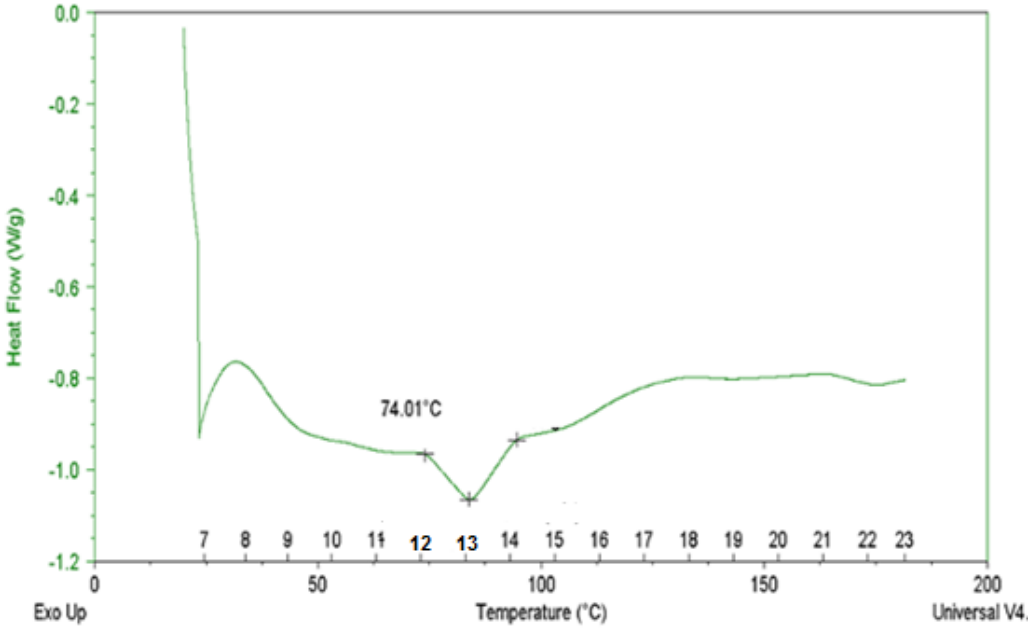



**Figure 3.8.** DSC result for PLG microcapsules prepares with 18% methanol.

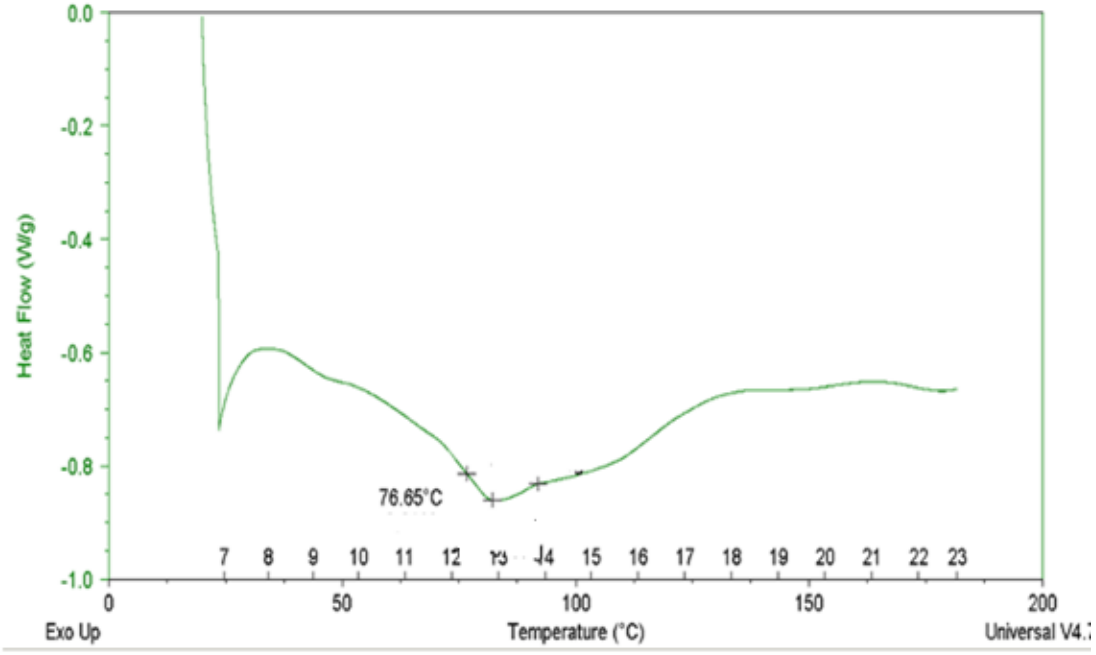



**Figure 3.9:** DSC result for PLG microcapsules prepares with 27% methanol.

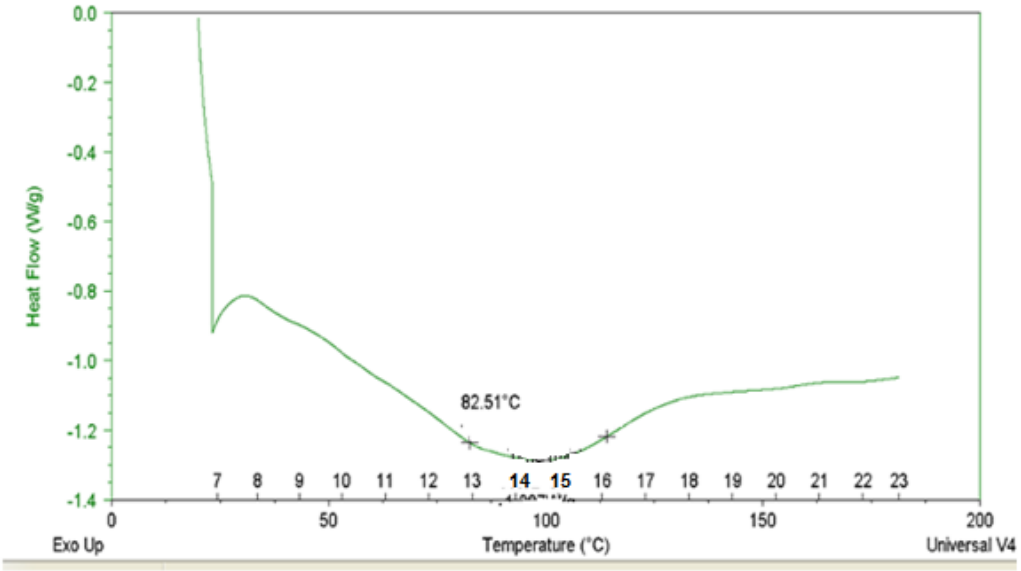



**Figure 3.10**: DSC result for PLG microcapsules prepares with 18% ethanol.

**Table 3. 1: $T_g$ and concentration of limonene release for PLG microcapsules prepared with different concentration of SDS, methanol and ethanol solutions**.

| PLG microcapsules prepared with | $T_g$ | Concentration of limonene release (g/g) (after 4 days). |
|---|---|---|
| 10% SDS | 75.7 $^oC$ | 0.0059 |
| 2% SDS | 71.3 $^oC$ | 0.0043 |
| 18% methanol | 74 $^oC$ | 0.0061 |
| 27% methanol | 76.6 $^oC$ | 0.0064 |
| 18% ethanol | 82.5 $^oC$ | 0.0063 |

Although the $T_g$ of microcapsules, prepared with more concentration of the nonsolvent, is higher than those prepared with less concentration of the nonsolvent and one would expect that the release would decrease with increasing the $T_g$, but the size of the microcapsules seems to be more dominant in this case and hence the release was faster with high concentration of the nonsolvent.

Our results show that as the concentration of the nonsolvent increases the size of PLG microcapsules decreases (see figures 3.1 and 3.3) and drug release increases.

## 3.5 Drug (limonene) release from PLG microcapsules.

### 3.5.1 The calibration curve of limonene.

UV-VIS spectrophotometer was used to determine the concentration of limonene released in time from the PLG microcapsules. A typical UV-VIS calibration curve for limonene in release buffer solution is shown in Figure 3.11.

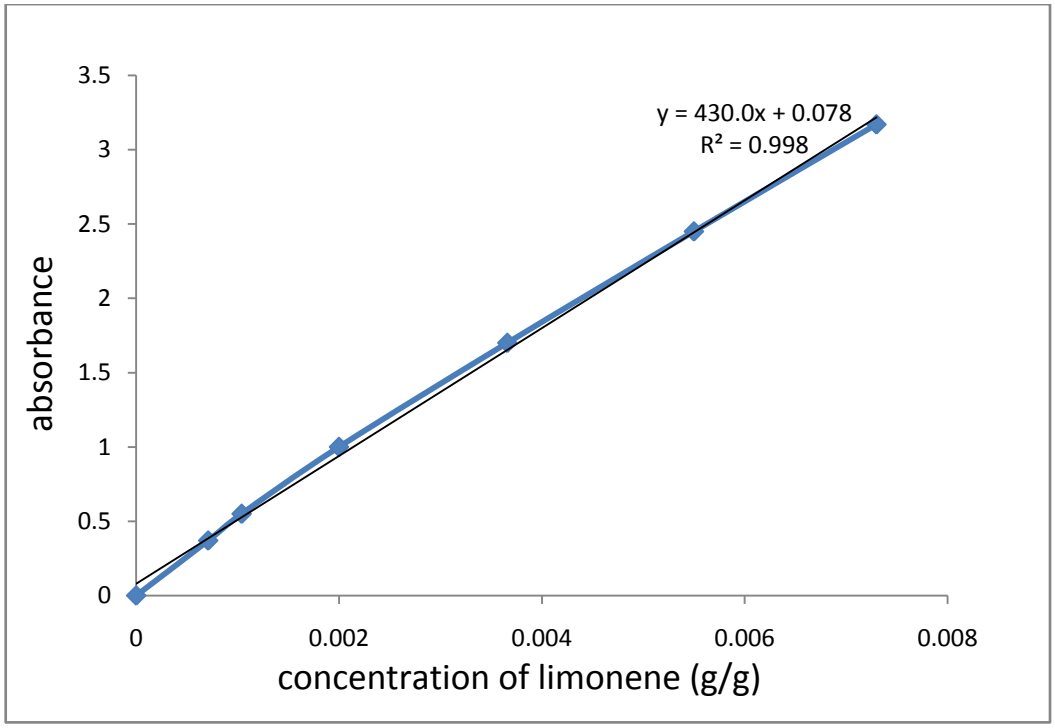



**Figure 3.11:** A typical calibration curve for limonene in 0 .1M potassium phosphate buffer analysis by UV-VIS spectrometric method.

The concentration of limonene release into the buffer solution with time was measured.

In this study the effect of SDS, methanol and ethanol concentrations on the limonene release from PLG microcapsules was studied and the obtained data are shown in Tables (3.2 – 3.8)

**Table 3.2: The concentration of limonene release (g/g) from PLG microcapsules with 10%SDS.**

| Time (days) | Absorbance | Concentration of limonene (g/g) |
|---|---|---|
| 1 | 2.21 | 0.0049 |
| 2 | 2.61 | 0.0059 |
| 3 | 2.74 | 0.0062 |
| 4 | 2.85 | 0.0064 |
| 6 | 3.02 | 0.0068 |
| 7 | 3.07 | 0.007 |
| 8 | 3.11 | 0.007 |
| 9 | 3.13 | 0.0071 |
| 10 | 3.15 | 0.0071 |

**Table 3.3: The concentration of limonene release (g/g) from PLG microcapsules with 5%SDS.**

| Time (days) | Absorbance | Concentration of limonene (g/g) |
|---|---|---|
| 1 | 1.92 | 0.0043 |
| 2 | 2.35 | 0.0053 |
| 3 | 2.56 | 0.0058 |
| 4 | 2.64 | 0.006 |
| 6 | 2.83 | 0.0064 |
| 7 | 2.92 | 0.0066 |
| 8 | 2.95 | 0.0067 |
| 9 | 2.98 | 0.0067 |
| 10 | 3.00 | 0.0068 |

**Table 3.4: The concentration of limonene release (g/g) from PLG microcapsules with 2%SDS.**

| Time (days) | Absorbance | Concentration of limonene (g/g) |
|---|---|---|
| 1 | 1.52 | 0.0034 |
| 2 | 1.91 | 0.0043 |
| 3 | 2.12 | 0.0047 |
| 4 | 2.25 | 0.0051 |
| 6 | 2.51 | 0.0057 |
| 7 | 2.6 | 0.0059 |
| 8 | 2.71 | 0.0061 |
| 9 | 2.82 | 0.0064 |
| 10 | 2.86 | 0.0065 |

**Table 3.5: The concentration of limonene release (g/g) from PLG microcapsules with 9% methanol.**

| **Time (days)** | **Absorbance** | **Concentration of limonene (g/g)** |
|---|---|---|
| 1 | 2.25 | 0.0051 |
| 2 | 2.62 | 0.0059 |
| 3 | 2.81 | 0.0064 |
| 4 | 2.90 | 0.0066 |
| 6 | 3.02 | 0.0068 |
| 7 | 3.08 | 0.007 |
| 8 | 3.10 | 0.007 |
| 9 | 3.10 | 0.007 |
| 10 | 3.10 | 0.007 |

**Table 3.6: The concentration of limonene release (g/g) from PLG microcapsules with 18%methanol.**

| Time (days) | Absorbance | Concentration of limonene (g/g) |
|---|---|---|
| 1 | 2.36 | 0.0053 |
| 2 | 2.71 | 0.0061 |
| 3 | 2.87 | 0.0065 |
| 4 | 2.96 | 0.0067 |
| 6 | 3.05 | 0.0069 |
| 7 | 3.11 | 0.007 |
| 8 | 3.11 | 0.007 |
| 9 | 3.11 | 0.007 |
| 10 | 3.11 | 0.007 |

**Table 3.7: The concentration of limonene release (g/g) from PLG microcapsules with 10%SDS and 27% methanol.**

| Time (days) | Absorbance | Concentration of limonene (g/g) |
|---|---|---|
| 1 | 2.43 | 0.0055 |
| 2 | 2.85 | 0.0064 |
| 3 | 2.95 | 0.0067 |
| 4 | 3.07 | 0.007 |
| 6 | 3.13 | 0.0071 |
| 7 | 3.13 | 0.0071 |
| 8 | 3.13 | 0.0071 |
| 9 | 3.13 | 0.0071 |
| 10 | 3.13 | 0.0071 |

**Table 3.8: The concentration of limonene release (g/g) from PLG microcapsules with 18% ethanol.**

| Time (days) | Absorbance | Concentration of limonene (g/g) |
|---|---|---|
| 1 | 2.41 | 0.0054 |
| 2 | 2.79 | 0.0063 |
| 3 | 2.89 | 0.0065 |
| 4 | 3.05 | 0.0069 |
| 6 | 3.10 | 0.007 |
| 7 | 3.13 | 0.0071 |
| 8 | 3.13 | 0.0071 |
| 9 | 3.13 | 0.0071 |
| 10 | 3.13 | 0.0071 |

### 3.5.2 Effect of the SDS Solution on the Limonene Release from PLG Microcapsules.

In this study limonene was used as a drug model, and it was encapsulated in PLG microcapsules. The release of limonene is determined with time for the different samples of PLG microcapsules, prepared with different concentrations of SDS solution, as shown in Figure 3.12.

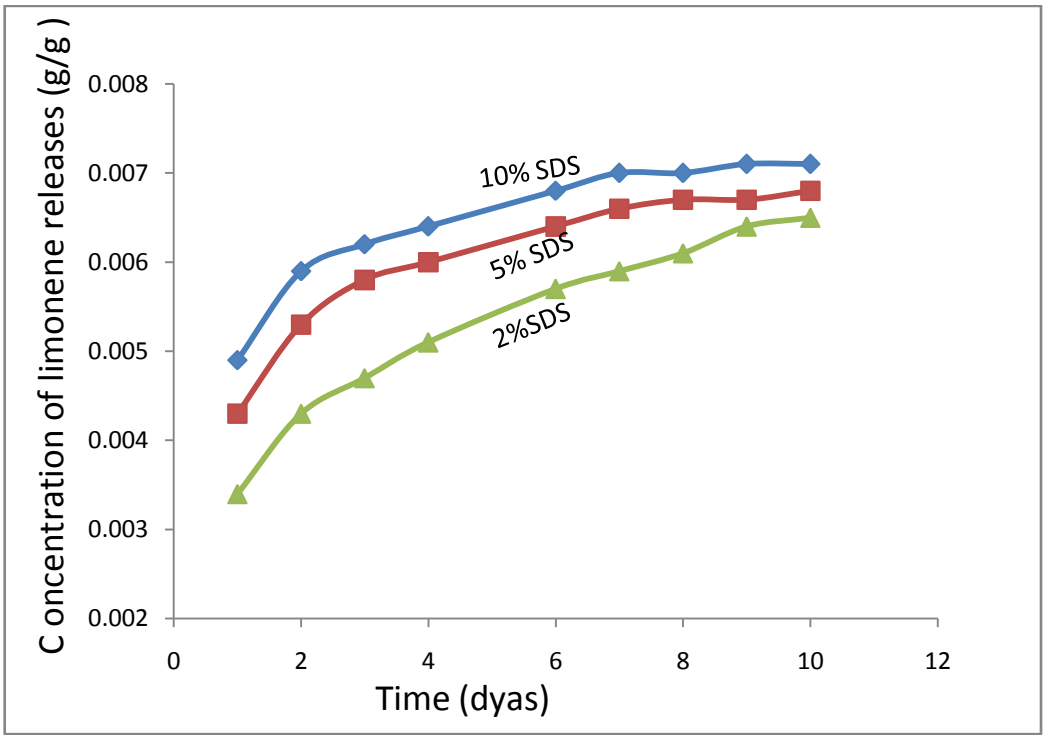



**Figure 3.12**: limonene release from PLG microcapsules prepared with different amount of SDS solution.

Figure 3.12 shows that the release behavior of limonene from the microcapsules is dependent on the SDS concentration; as the concentration of SDS solution increases, the concentration of limonene release from PLG microcapsules increases. For instance, after a release time of 4 days, the total limonene release increased from 0.0051 (g/g) with 2% SDS to 0.006 (g/g) when 5% SDS solution was used and when 10% SDS was used the release become 0.0064 (g/g). This might be related to the difference in the size of the microcapsules obtained with changing the SDS concentration as illustrated in Figure 3.1. The increase in the concentration of SDS solution decreases the size of PLG microcapsules and the surface area-to-volume ratio of the microcapsules consequently increases, thus the diffusion flux of limonene from microcapsules increased [9, 61, 62, 63].

Kim et.al [9] studied the effect of some factors such as the size and molecular weight of microcapsules of polyanhydride and polycaprolactone polymers on drug release; they found that as the size decreases of polymer microcapsules, the drug release increases.

Pachuau et.al [61] studied the effect of the Tween 80 surfactant on the size and drug release from ethyl cellulose microcapsules; they found that as the content of surfactant increases, the size decrease and the drug release increase of polymer microcapsules.

Park et.al [62] studied the effect of erythromycin estolate emulsifier on the size and drug release from Poly (ε-caprolactone) microcapsules and the release of drug was studied by using UV-visible spectroscopy. They found that as the emulsifier content increases, the size of microcapsules decreases and the drug release increases.

Assimopoulou et.al [63] studied the effect of SDS solution on shikonin drug release from ethyl cellulose microcapsules; they found that as the SDS concentration increases the drug release from microcapsules increases.

Our results show that when the concentration of SDS solution increases in the process of prepearing PLG microcapsules, the size of microcapsules decreases and the limonene release increases with time from microcapsules, this is accordance with previous studies [61, 62, 63] .

### 3.5.3 Effect of the Type and Concentration of Alcohols in the Nonsolvnet on Limonene Release.

As far as we know, this is the first study of the effect of the type and concentration of alcohols in the nonsolvnet on drug release from polymer microcapsules.

Figure 3.13 shows the amount of limonene released as a function of time from different PLG microcapsules prepared with different methanol concentration in the nonsolvent.

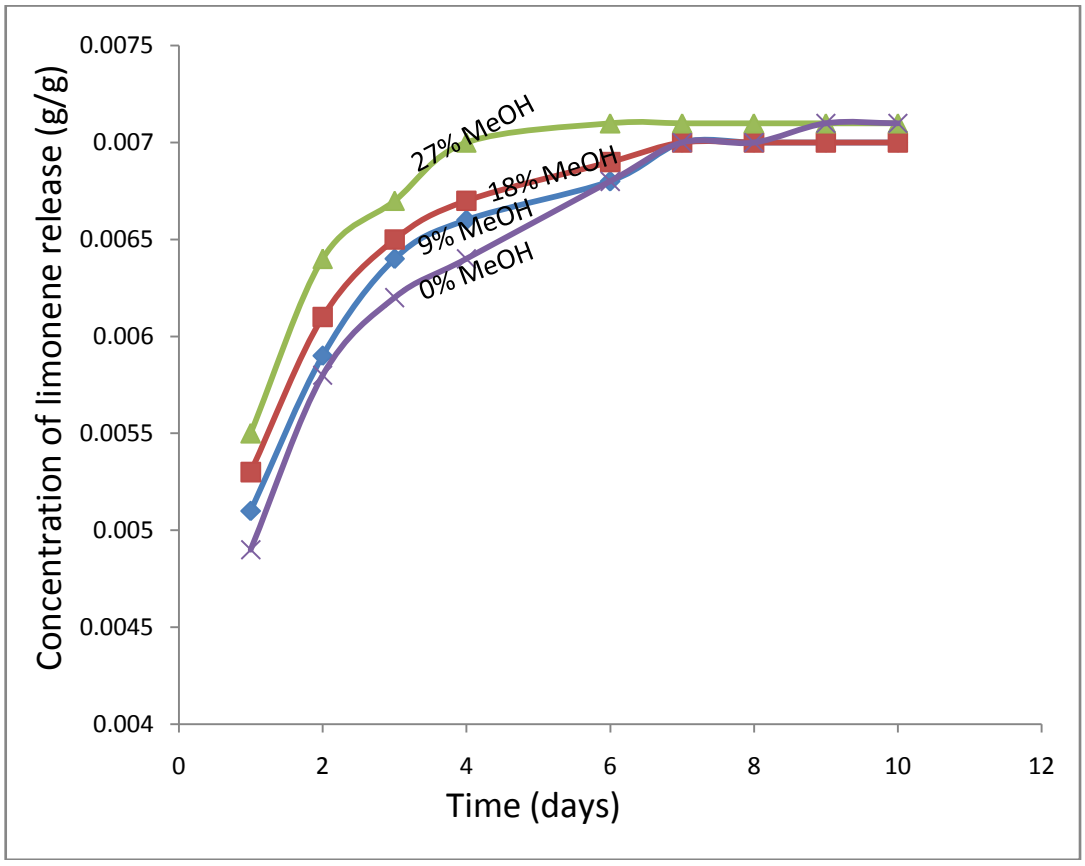



**Figure 3.13:** Limonene release from PLG microcapsules prepared with different amount of methanol solutions.

As can be seen from the Figure 3.13 that for all formulations, the limonene release increases exponentially in the first few days and after that, it

reaches plateau. One can clearly see that the rate of limonene release increases with increasing methanol concentration and the plateau was reached earlier.

For instance, the maximum amount of limonene release of (0.007 g/g) was attained after 8 days with water and that was reduced to only 4 days with 27% methanol. This could be attributed to the difference in the size of the microcapsules; increasing methanol concentarion decreases the size of the microcapsules (see Figure 3.3) which increases the total surface area of the capsules available for release hence the rate of limonene transfer increases [9, 61, 62, 63].

Figure 3.13 shows that when 27% methanol was used in process of preparing microcapsules, the concentration of limonene release from microcapsules was bigger than the concentration of limonene release when 18% methanol was used, and when methanol was 9% the release decreased compared to 18% and 27% methanol.

From the above discussion in the process of preparing microcapsules, as the concentration of methanol increases, the size of microcapsules decreases and the limonene release from microcapsules increases.

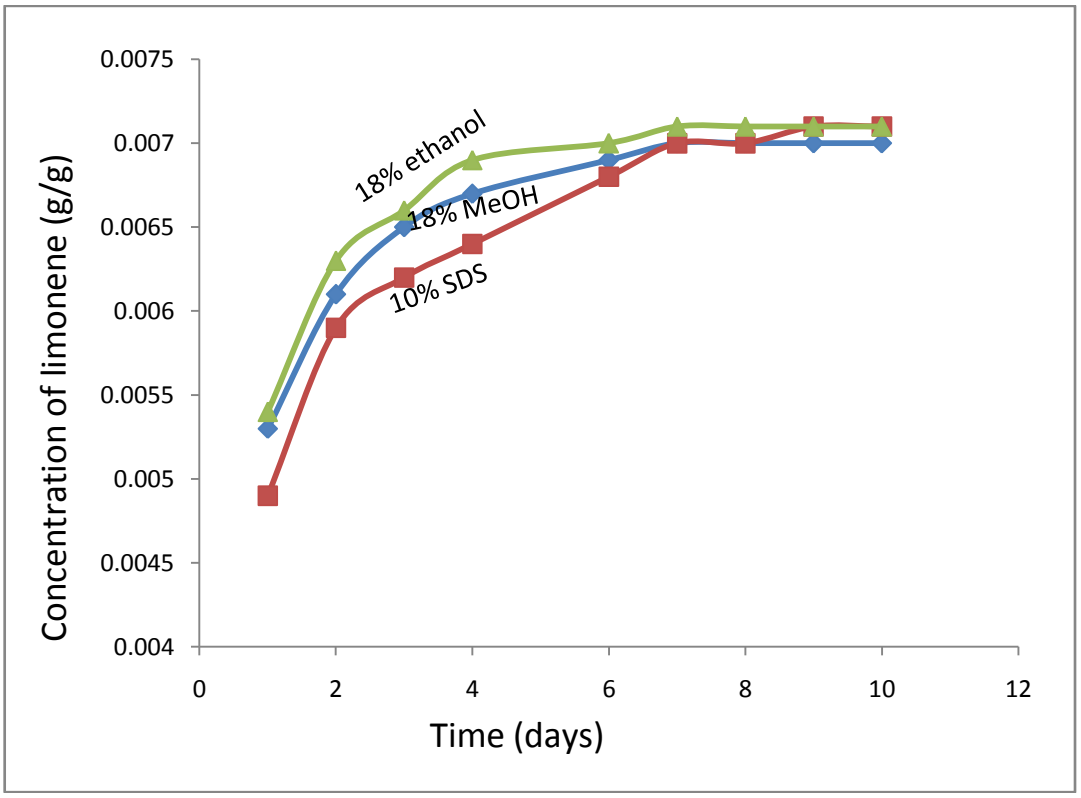



**Figure 3.14.** Limonene release from PLG microcapsules prepared with amount of methanol, ethanol solutions

Figure 3.14. shows that when 18% of ethanol was used, the limonene release was faster than with18% of methanol.

This is because the particles prepared with ethanol were smaller in size than those prepared with methanol [44]. Although the $T_g$ of microcapsules prepared with ethanol is higher than those prepared with methanol and one would expect that the release would decrease with increasing the $T_g$ [45, 64], but the size of the microcapsules seems to be more dominant in this case and hence the release was faster with ethanol.

Ethanol increases the viscosity and decreases the interfacial tension of the nonsolvent more than methanol and as the viscosity increases and interfacial tension decreases, the size of microcapsules decreases, then the

drug release from microcapsules with ethanol will be more than drug release from methanol. [9, 44].

## Conclusion

1 – PLG microcapsules were successfully prepared using traditional emulsification method.

2 - The size of the microcapsules is quite polydisperse.

3 - In the process of preparing PLG microcapsules, the size of PLG microcapsules prepared decreases with increasing the concentration of nonsolvent solution such as SDS solution, methanol and ethanol.

4 - The limonene release from PLG microcapsules prepared was increased with increasing the concentration of nonsolvent solution.

5 – The limonene release rate was affected by the type of alcohol used, PLG microcapsules prepared in the presence ethanol show higher release rate than those prepared in the presence of methanol.

6 – The $T_g$ of PLG microcapsules increase with increasing the concentration of the nonsolvent solutions.

7- PLG is biodegradable polymer that has a slow degradation rate and high permeability to small drug molecules.

## Suggestions for Future Work:

1- Studying the release of drugs from other polymer microcapsules.

2 - Studying the effect of another surfactant such as poly (vinyl alcohol) on the size of polymer microcapsules and drug release from polymer microcapsules.

3 – Preparation of nanoparticles of polymer microcapsules by increasing the concentration of nonsolvnet in the process of preparing of polymer microcapsules.

4 – Studding the drug release from nanoparticles of polymer microcapsules.

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# Appendix

The tables below show the size of PLG microcapsules prepared with different nonsolvent.

**Table 1: The size of PLG microcapsules prepared with 10%SDS solution.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 3 | 3.49 |
| 1 | 3.67 |
| 1 | 3.84 |
| 1 | 4.01 |
| 1 | 4.19 |
| 1 | 4.2 |
| 2 | 4.54 |
| 2 | 4.88 |
| 1 | 4.9 |
| 1 | 5.06 |
| 1 | 5.41 |
| 1 | 5.58 |
| 1 | 5.76 |
| 2 | 5.93 |
| 1 | 6.11 |
| 3 | 6.28 |
| 1 | 6.3 |
| 1 | 6.45 |
| 2 | 6.63 |
| 1 | 6.81 |
| 1 | 6.98 |
| 3 | 7.33 |

| | |
|---|---|
| 2 | 7.5 |
| 4 | 7.7 |
| 1 | 7.85 |
| 1 | 8.03 |
| 2 | 8.2 |
| 2 | 8.38 |
| 1 | 8.73 |
| 1 | 9.08 |
| 1 | 9.11 |
| 1 | 9.25 |
| 1 | 9.43 |
| 1 | 9.6 |
| 1 | 9.77 |
| 1 | 10.12 |
| 1 | 10.3 |
| 1 | 10.5 |
| 1 | 11.17 |
| 2 | 11.69 |
| 1 | 12.57 |
| 1 | 14 |
| 1 | 17.63 |

**Table 2: The size of PLG microcapsules prepared with 5%SDS solution.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 1 | 4.71 |
| 1 | 6.8 |
| 1 | 7 |
| 1 | 7.43 |
| 1 | 7.68 |
| 1 | 8.03 |
| 1 | 9.25 |
| 1 | 10.3 |
| 1 | 10.5 |
| 1 | 10.82 |
| 2 | 11 |
| 1 | 11.17 |
| 1 | 11.35 |
| 1 | 11.52 |
| 2 | 11.69 |
| 1 | 12.04 |
| 1 | 12.22 |
| 1 | 12.39 |
| 1 | 12.53 |
| 1 | 12.6 |
| 1 | 13.09 |
| 1 | 13.27 |
| 1 | 13.44 |
| 2 | 13.73 |
| 2 | 13.96 |

| | |
|---|---|
| 1 | 14 |
| 1 | 14.66 |
| 2 | 15.01 |
| 1 | 15.53 |
| 1 | 16.58 |
| 1 | 17.45 |
| 1 | 17.98 |
| 1 | 18.85 |
| 1 | 19.2 |
| 1 | 19.91 |
| 1 | 20.77 |
| 1 | 20.95 |
| 1 | 21.12 |
| 1 | 21.65 |
| 2 | 22.52 |
| 1 | 23.1 |
| 1 | 23.74 |
| 1 | 24.09 |
| 1 | 25.31 |
| 1 | 37.88 |

**Table 3: The size of PLG microcapsules prepared with 2%SDS solution.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 1 | 7.01 |
| 1 | 11 |
| 1 | 11.4 |
| 1 | 11.52 |
| 1 | 12.2 |
| 1 | 12.52 |
| 1 | 12.98 |
| 2 | 14.14 |
| 1 | 14.35 |
| 1 | 14.49 |
| 1 | 14.69 |
| 1 | 14.97 |
| 2 | 15.3 |
| 1 | 15.69 |
| 1 | 16.1 |
| 1 | 16.42 |
| 1 | 17.53 |
| 1 | 18.68 |
| 1 | 19.21 |
| 1 | 20.23 |
| 2 | 21.21 |
| 1 | 22.34 |
| 1 | 22.65 |
| 1 | 24.26 |

| | |
|---|---|
| 1 | 24.67 |
| 2 | 25.14 |
| 2 | 26.18 |
| 1 | 26.7 |
| 2 | 26.87 |
| 1 | 30.37 |
| 1 | 31.2 |
| 2 | 34.5 |
| 1 | 36.14 |
| 1 | 36.89 |
| 2 | 37.06 |
| 1 | 40.2 |
| 2 | 41.12 |
| 1 | 44.41 |
| 1 | 52.59 |
| 1 | 53.45 |
| 1 | 55.59 |

**Table 4: The size of PLG microcapsules prepared with 9% methanol from the nonsolvent.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 1 | 1.75 |
| 1 | 2.1 |
| 2 | 2.45 |
| 1 | 2.96 |
| 1 | 3.14 |
| 2 | 3.32 |
| 1 | 3.67 |
| 1 | 4.19 |
| 3 | 4.36 |
| 4 | 4.54 |
| 3 | 4.71 |
| 2 | 4.88 |
| 3 | 5.23 |
| 1 | 5.58 |
| 2 | 5.76 |
| 2 | 6.11 |
| 1 | 6.3 |
| 1 | 6.45 |
| 1 | 6.63 |
| 1 | 7 |
| 1 | 7.16 |
| 1 | 7.33 |
| 1 | 7.85 |
| 2 | 8.03 |

| | |
|---|---|
| 3 | 8.4 |
| 3 | 8.55 |
| 1 | 8.73 |
| 2 | 9.1 |
| 1 | 9.25 |
| 1 | 9.6 |
| 1 | 9.77 |
| 1 | 9.95 |
| 2 | 10.3 |
| 3 | 10.5 |
| 1 | 10.82 |
| 1 | 10.99 |
| 1 | 11.17 |
| 1 | 11.69 |
| 1 | 12.04 |
| 1 | 12.6 |
| 1 | 13.44 |
| 1 | 14.49 |
| 1 | 15.19 |
| 1 | 15.71 |

**Table 5: The size of PLG microcapsules prepared with 18% methanol from the nonsolvent.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 3 | 2.26 |
| 3 | 2.44 |
| 3 | 2.61 |
| 4 | 2.8 |
| 1 | 2.96 |
| 2 | 3.5 |
| 1 | 3.67 |
| 1 | 4.01 |
| 4 | 4.2 |
| 1 | 4.36 |
| 3 | 4.54 |
| 3 | 4.71 |
| 9 | 4.9 |
| 3 | 5.24 |
| 1 | 5.41 |
| 6 | 5.58 |
| 4 | 5.93 |
| 2 | 6.3 |
| 1 | 6.45 |
| 1 | 6.63 |
| 2 | 6.81 |
| 1 | 6.98 |
| 1 | 7.16 |

**Table 6: The size of PLG microcapsules prepared with 27% methanol from the nonsolvent.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 1 | 1.22 |
| 2 | 1.58 |
| 7 | 1.75 |
| 6 | 1.92 |
| 6 | 2.09 |
| 7 | 2.26 |
| 3 | 2.44 |
| 4 | 2.61 |
| 3 | 2.79 |
| 2 | 2.96 |
| 2 | 3.14 |
| 5 | 3.31 |
| 3 | 3.49 |
| 1 | 3.67 |
| 3 | 3.84 |
| 1 | 4.19 |
| 1 | 4.71 |
| 1 | 4.89 |
| 1 | 5.06 |

**Table 7: The size of PLG microcapsules prepared with 18% ethanol from the nonsolvent.**

| number of microcapsules | size of microcapsules (μm) |
|---|---|
| 1 | 1.23 |
| 3 | 1.92 |
| 3 | 2.1 |
| 3 | 2.26 |
| 6 | 2.44 |
| 3 | 2.62 |
| 5 | 2.79 |
| 5 | 2.96 |
| 3 | 3.14 |
| 2 | 3.32 |
| 4 | 3.49 |
| 4 | 3.67 |
| 1 | 3.84 |
| 4 | 4.01 |
| 2 | 4.36 |
| 1 | 4.54 |
| 1 | 4.89 |
| 2 | 5.06 |
| 1 | 5.23 |
| 4 | 5.41 |
| 2 | 5.58 |
| 1 | 5.67 |
| 1 | 5.76 |
| 1 | 6.46 |
| 1 | 6.98 |
| 1 | 9.08 |
| 1 | 9.25 |

كلية الدراسات العليا

جامعة النجاح الوطنية

# كريات مبلمر دل- لاكتايد كو- جلايكولايد القابل للتحلل الحيوي ككبسولات لتفريغ الدواء

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إشراف

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قدمت هذه الأطروحة استكمالاً لمتطلبات درجة الحصول على الماجستير في الكيمياء بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس- فلسطين.

2014

**كريات مبلمر دل–لاكتايد كو–جلايكولايد القابل للتحلل الحيوي ككبسولات لتفريغ الدواء**

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## الملخص

مبلمر دل–لاكتايد كو–جلايكولايد هو مبلمر قابل للتحلل الحيوي في الجسم ، وغير سام كما انه يستخدم ككبسولات لتفريغ الدواء في الجسم .

في هذه الدراسة تم تحضير كبسولات من هذا المبلمر بحجم المايكرو باستخدام مواد غير مذيبة مثل الميثانول والايثانول، وتم دراسة تأثير هذه المواد على حجم المايكروكابسول المحضرة وعلى تركيز تفريغ الليمونين من الكبسولات المحضرة .

كما تم تحضير كبسولات من المبلمر تحتوي على ليمونين لدراسة تفريغ الليمونين مع الزمن من الكبسولات المحضرة باختلاف تركيز المواد الغير مذيبة .

وقد تم تشخيص الكبسولات المحضرة من المبلمر باختلاف تركيز المواد غير المذيبة لمعرفة حجم الجزيئات وشكلها، والأجهزة التي استخدمت للتشخيص هي light microscope, SEM كما تم قياس تفريغ الليمونين من الكبسولات المحضرة عند درجة حرارة تساوي 37 درجة سليسيوس ودراسة تأثير المواد غير المذيبة على تفريغ الليمونين من الكبسولات المحضرة باختلاف. UV-VIS spectrophotometer تركيز المواد غير المذيبة باستخدام جهاز اظهرت النتائج انه كلما زاد تركيز المواد غير المذيبة في عملية تحضير الكبسولات من المبلمر فان حجم الكبسولات يصغر اكثر كما ان تركيز الليمونين (Methanol,ethanol,SDS ) مثل الخارج من الكبسولات يزداد، وذلك بسبب انه كلما زاد تركيز المواد غير الذائبة كلما زادت اللزوجة وقل التوتر السطحي مما يقلل حجم الكبسولات المحضرة ويزيد من تفريغ الليمونين مع الزمن .

كما تبين ان تاثير الايثانول على حجم كبسولات المبلمر كان اكبر من تاثير الميثانول حيث اصبحت اصغر عند استخدام الايثانول  كما ان تركيز تفريغ الليمونين ازداد عند استخدام الايثانوا بدل الميثانول.