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Microencapsulation of the Non-Steroidal Anti-Inflammatory Drugs into Biodegradable Polymers Using Supercritical Fluid Technology

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A thesis submitted to
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Dedication

I dedicate this work to my Grandfather and my Father's souls may God rest them in peace. Special dedication to my mother for the ultimate support she gave me, today this degree is to say thank you and be proud of your product.

Acknowledgment

In the name of Allah most gracious and most merciful. I would like to thank Allah for the blessings and that he give the courage and faith to believe in me and in the gifts that he gave so I could complete this work.

There can be no doubt that my advisors Dr. Ali Al-Marzouqi was the key indicator accomplishing this work successfully. Special thanks to Dr. Mahmood Mohsin co-supervisor for making this work easier for me and for they both gave me the support, advices and directions that lead to achieve this degree.

Many thanks to my family members and friends for their support and prays through this journey. A lot of respect and thanks to UAEU staff in the Faculty of Medicine (microscope laboratory), Chemistry Department and Chemical and Petroleum Engineering Department who helped me accomplish the different parts.

Abstract

Osteoarthritis is a disease that attacks human bones especially in older people and usually non-steroidal anti-inflammatory drugs (NSAIDS) are being prescribed for patients with Osteoarthritis. These kinds of drugs usually have low aqueous solubility and in order to have their therapeutic effects, their solubility should be enhanced. The purpose of this study was to find solution for this problem and one way to do that is to reduce the particle size by forming microparticles. In this project, one of these types of drugs ibuprofen (isobutyl-propanoic-phenolic Acid) was encapsulated into a polymer (PVP polyvinylpyrrolidone) using supercritical fluid technology (Supercritical CO_2) to form drug-polymer microparticles. Another aim was to measure the solubility, dissolution rate and surface characteristics of the prepared drug-polymer microparticles by characterizing them using various characterization techniques such as fourier transform infrared spectroscopy (FTIR), ultraviolet spectroscopy (UV), transmission electron microscopy (TEM), scanning electron microscope (SEM), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Various drug-polymer formulations were prepared depending on various administrative dosages. Different conditions (i.e. different temperatures, pressures, flow rates and different drug solution:CO_2 volume ratio) were tested in preparing drug-polymer microparticles. Results from TEM images and FT-IR graphs show that microparticles were successfully prepared. Different conditions gave different shapes of drug-polymer microparticles in the SEM results. Finally dissolution rate of the drug-polymer microparticles in the simulated gastric fluid showed promising results.

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Chapter I

Introduction

1.1. Osteoarthritis disease:

Bone diseases are common especially nowadays due to the rhythm of today's lifestyle, the long working hours relative to resting hours and type of food we consume. Osteoarthritis (OA) is a well-known disease, which comes as a consequent of aging process and is regarded as one of the most common diseases among humans. This musculoskeletal disorder has not only been described in mammals of many ages, but also it goes back to the Egyptian mummies and in the dinosaur's era, its exact etiology is far from being fully understood. As the world population is growing, it is of the utmost importance to find out more about the pathogenesis of the disease and thus allow the discovery of new treatments to stop or prevent its progression.

Osteoarthritis is also the most common form of arthritis; it is affecting millions of people all over the world. It is a complex disease whose etiology bridges biomechanics and biochemistry. It has been proven that systemic factors (such as genetics, dietary intake, estrogen use, and bone density) and local biomechanical factors (such as muscle weakness, obesity, and joint laxity) are causes of this disease. Evidence is growing for the role of these two factors and modifying them has lightened the road for prevention of osteoarthritis-related pain and disability. Major advances in management to reduce pain and disability are yielding full array of available treatments ranging from nutriceuticals to chondrocyte transplantation, new oral anti-inflammatory medications and health education (1).

Mechanical and biochemical factors are combined and globally observed in OA (2). The disease process affects not only the cartilage, but also the entire joint structure, including the synovial membrane, subchondral bone, ligaments, and periarticular muscles. There are some changes in OA synovium, the inflammatory happens as synovial hypertrophy and hyperplasia with an increased number of lining cells, and also an infiltration of the sublining tissue with a mixed population of inflammatory cells. In patients with severe disease, the extent of inflammation can sometimes reach that observed in rheumatoid arthritis (RA) patients at the clinical stage (3). Synovial inflammation is clearly reflected in many of the signs and symptoms of OA, including joint swelling and effusion, stiffness, and sometimes redness.

The main objectives in the management of OA are to reduce the symptoms, minimize functional disability, and limit progression of the structural changes. Scientists have been searching and tried to understand the role of catabolic factors in cartilage degradation and the implication of synovial inflammation in the last two decades (4). These findings have made possible more precise identification of pathways that have the potential to become therapeutic targets.

Clinical studies to date have focused on the alleviation of signs and symptoms of mild-to-moderate OA cases using nonsteroidal anti-inflammatory drugs (NSAIDs) (5). Published data on intraarticular corticosteroids in OA have demonstrated short-term (up to 4 weeks) improvement of signs and symptoms compared with placebo (6).

1.2.Nonsteroidal Anti-Inflammatory Drugs (NSAID's):

Non-steroidal anti-inflammatory drugs are usually abbreviated to NSAIDs or NAIDs, but also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs). They are drugs with analgesic and antipyretic (fever-reducing) effects, which have in higher doses anti-inflammatory effects (7), analgesic, and antipyretic effects and inhibit thrombocyte aggregation. The drugs have no documented effect on the disease process itself (8).

A survey conducted for the World Health Organization (WHO) reported that one adult in five suffers from chronic non-malignant pain, which mostly occurs in the back, head, joints and limbs. More than 15% of the worldwide population suffers from some form of osteoarthritis, and this incidence is even higher in elderly people. As the world population is growing older, this incidence will continue to rise (9). Nonsteroidal anti-inflammatory drugs (NSAIDs) have become one of the most commonly used medications in Western nations since the introduction of the first NSAID and aspirin about one century ago. It is estimated that more than 70 million NSAID prescriptions and more than 30 billion of over-the-counter aspirin, ibuprofen, ketoprofen, and naproxen preparations are sold annually in the United States alone. Although NSAIDs are generally well tolerated; their use frequently is limited by adverse gastrointestinal

effects ranging from dyspepsia to serious complications, such as swelling bleeding or perforation from gastric or duodenal ulcers (10).

1.2.1. Solubility of NSAIDs

A common limitation with NSAIDs is their solubility. According to the established statistics, about a third of the drugs listed in the United States Pharmacopeia are poorly water-soluble or insoluble and more than 40% of new drug development has failed because of poor biopharmaceutical properties. Various techniques have been developed to address the solubility issue, including micronization, surfactant-aid dispersion, the use of organic solvents, emulsions and microemulsions, solid dispersion technology and carriers based on polymers and liposomes (11-16).

The search continues for more effective and versatile techniques applicable to the formulation of drugs with difficulty in aqueous solubility. The nanosizing of drug particles has been identified as a potentially effective and broadly applicable approach, with implications beyond the mitigation for water insolubility. For example, smaller-diameter particles correspond to a faster dissolution rate, thus potentially higher activity and easier absorption. Other distinct advantages of nanosizing of the drug particles include tissue or cell specific targeting of drugs, longer circulating capacity in the blood, higher stability against enzymatic degradation, and the reduction of unwanted side effects (17-20).

1.2.2. Types of NSAIDs

NSAIDs can be classified based on their chemical structure or mechanism of action. Earlier types of NSAIDs were known long before their mechanism of action was discovered and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action. For example salicylates (e.g. Aspirin (acetylsalicylic acid)), propionic acid derivatives (e.g. Ibuprofen), acetic acid derivatives (e.g. Diclofenac, enolic acid (Oxicam) derivatives (e.g. Piroxicam), fenamic acid derivatives (Fenamates) (e.g. Mefenamic acid), selective COX-2 inhibitors (Coxibs) (e.g. Parecoxib) and sulphonanilides (e.g. Nimesulide) have a little difference in clinical efficacy when used at equivalent doses, and the

differences among compounds tend to be within the range of dosing regimens (related to the compound's elimination half-life), route of administration and tolerability profile.

In this work ibuprofen, which has the IUPAC nomenclature of 2-(p-isobutylphenyl)propanoic acid was used as a model nonsteroidal anti-inflammatory drug. Ibuprofen is used for relief of symptoms of arthritis, fever (21) and also as an analgesic agent for pain, especially where there is an inflammatory component. Ibuprofen has the following chemical structure:

Ibuprofen is a core medicine in the World Health Organization's "WHO Model List of Essential Medicines", which is a list of minimum medical needs for a basic healthcare system (22). Ibuprofen is also being used primarily for fever inflammatory diseases such as rheumatoid arthritis. It works by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H_2 (PGH_2) which in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation and fever) (23).

Ibuprofen was derived from propionic acid by the research team of Boots Group during the 1960s (24). It was discovered by Andrew RM Dunlop and his colleagues and the drug was launched as a treatment for rheumatoid arthritis in the United Kingdom in 1969, and in the United States in 1974.

1.3. Biodegradable Polymers

The use of polymer-based drug delivery systems in medical therapies is of growing interest. Synthetic biodegradable polymers that can be applied without causing undesirable effects to living systems (*in vivo*) are now popular choices to eliminate problems with some drugs that have a narrow therapeutic range. Biodegradable polymers are commonly used as materials for drug delivery systems because their permeability and diffusivity can be modified and controlled. They can be shaped easily by a large variety of processing methods. Biodegradable polymers are used in sutures, medical treatment of bone fractures and more recently as carriers of drugs in controlled-release preparations (25-26). Biodegradable polymers have offered scientists a possible solution to waste-disposal problems associated with traditional petroleum-derived plastics (26). Biodegradation is defined as an event which takes place through the action of enzymes and/or chemical decomposition associated with living organisms (bacteria,

fungi, etc.) and their secretion products (27). It is also necessary to consider biotic reactions like photodegradation, oxidation and hydrolysis which may also alter the polymer before, during or instead of biodegradation because of environmental factors.

Biodegradable polymers can be used as controlled drug delivery systems of bioactive agents and drugs. They can be used for this purpose in form of films, sponges, microspheres and nanoparticles. However, the most interesting route seems to be the use of micro and nanoparticles. Among biodegradable polymers, natural polymers promise better drug delivery efficiency, a reduced toxicity and an improvement of patient compliance (28). Controlled drug delivery products, using biocompatible or biodegradable polymers, have received considerable attention in the past years. These substances provide in general a more controlled rate of dissolution of the drug inside the body which will improve its therapeutic action. In fact, there is a growing interest of the pharmaceutical industry in the development of these systems (29).

1.3.1. Physical properties of polymers in supercritical CO_2

Polymers are usually swollen in a supercritical atmosphere due to the interactions between polymer and supercritical CO_2.
are used to study the specific intermolecular interactions between supercritical CO_2 and the polymers (30). Polymers usually consist of long chains while oligomers are made of short ones which will affect the chain flexibility. The chain flexibility of polymers can aid dissolution in supercritical CO_2, carbonyl or ether groups that are accessible in the backbone or on side chains can specifically interact with supercritical CO_2 (e.g. PLA). Also polymers with ether groups (e.g. polyethylene glycol (PEG)) showed stronger interaction than polyesters due to weak Lewis acid–base interaction in polyesters (31).

1.3.2. Solubility of CO_2

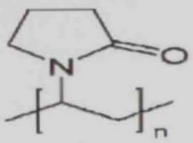
Molecular structure (the interaction between CO_2 and molecular chains) and the morphology (crystalline or amorphous, related with free volume) of polymers will influence CO_2 solubility and diffusivity. The solubility of CO_2 in many polymers, (e.g. poly methyl methacrylate

(PMMA) and poly-styrene (PS)), has been studied by evaluating CO_2 sorption and polymer swelling (36-38). There was a general perception that sorption and swelling is a purely physical phenomenon until Fourier transform-infrared (FTIR) and ATRIR spectroscopy were used to study the specific intermolecular interactions between CO_2 and polymers (39-41).

Although poly(lactic acid) (PLA) and poly (lactic acid-co-glycolic acid) (PLGA) have the same chemical structure in the main chains, the steric hindrance close to the carbonyl group and accessible free volume caused by methyl pendant groups can lead to their different behavior of solubility and interaction. In the case of PLGAs, some methyl groups are substituted with hydrogen atoms which cause much less hindrance for the interaction with the supercritical CO_2. However, the accessible polymers free volume was found to have a greater effect on solubility than the interaction between polymers and CO_2 (32). Therefore, the solubility of CO_2 in PLGA copolymers decreases with the increase in the glycolic acid content.

1.3.3 Polymer utilized in this research

Polyvinylpyrrolidone (PVP), which is a water-soluble polymer was used in this study. PVP is also called polyvidone and it has the following chemical structure:



One of the salient features of PVP is its universal solubility, which extends from the extremely hydrophilic solvents such as water to hydrophobic liquids such as butanol. Today the use of organic solvents such as methylene chloride or chloroform is severely restricted, but nevertheless small quantities of organic solvents are still used by most pharmaceutical companies. Polyvinylpyrrolidone has been used in pharmaceuticals such as ointments, disinfectants, surgical scrubs or as a binder in many pharmaceutical tablets (42) and it simply passes through the body when taken orally.

1.4. Microencapsulation methodologies

The main purpose of micronizing drug/polymer systems is to enhance the drug delivery. Controlled drug delivery occurs when a polymer/drug system is designed to release the drug in a predetermined manner as shown in Figure 1. In other words, controlled release systems are used to achieve a more effective therapy, i.e., a system with a delivery profile that would yield a high drug level in the blood over a long period of time, avoiding the large fluctuations in drug concentration and to reduce the need of several administrations (52). In many cases, conventional drug delivery products provide sharp increases in the drug concentration at potentially toxic levels, followed by a relatively short period at the therapeutic level and drug concentration drops until new administration as shown in Figure 1a (53).

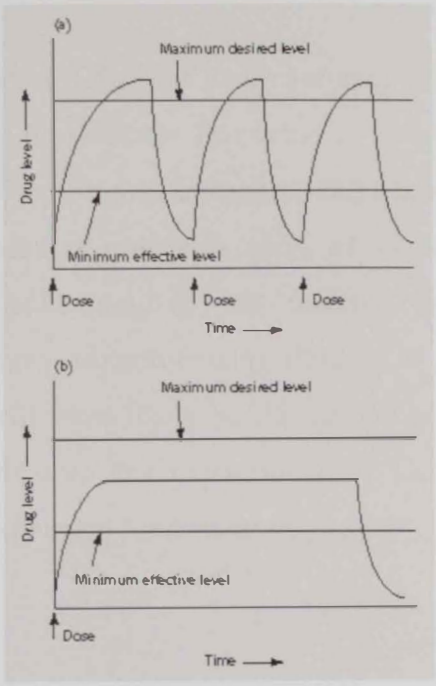


Figure 1. Drug levels in the blood with (a) traditional drug dosing and (b) controlled-delivery dosing

Micro- and nanoparticles composed of a biologically active compound, and a biodegradable polymer acting as a carrier, represent one of the most studied systems in the research for new drug delivery systems (54). In such formulations, the polymer enhances the pharmacological

features of the drug such as solubility in the gastric fluid and stability. Depending on the degradation rate of the biocompatible polymer, the polymer also enhances the controlled release of the drug hence reducing the number of required doses (55) as shown at Figure 1b.

1.4.1. Conventional microencapsulation methods

Several traditional particle size reduction or microencapsulation techniques such as mechanical milling, emulsion and precipitation–condensation methods have found some success in the preparing drug nanoparticles, but issues including the broad particle size distribution in products and the excessive use of organic solvent remain to be addressed.

1.4.2. Supercritical Fluid Technology

Interest in supercritical fluids (SCFs) and their potential use for process improvements has significantly increased in the past decade. Properties of these fluids can be tuned by changing the fluid density between those of liquid and gases. SCFs have been adopted as: (a) alternative solvents for classical separation processes such as extraction, fractionation, adsorption, chromatography, and crystallization, (b) as reaction media as in polymerization or depolymerization, or (c) simply as reprocessing fluid as in production of particles, fibres, or foams. Particle formation will most likely be the second major commercial application area that uses supercritical fluids after the extraction (50). Carbon Dioxide (CO_2) is the most commonly used fluid in supercritical fluid technologies.

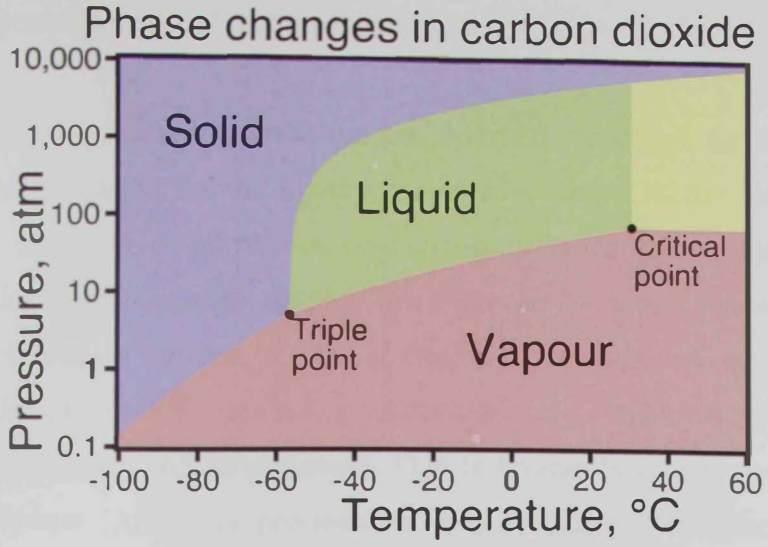


Figure 2. Phase diagram of supercritical CO_2

Some of the advantages of supercritical CO_2 are its mild operation condition (critical temperature and pressure of 31°C and 7.38MPa, respectively) Figure 2, gaseous standard state under ambient conditions, nontoxicity and it's relatively low cost compared to organic solvents. The favourable physical and chemical properties of CO_2 are some of the reasons why so many applications that use supercritical CO_2 focus on pharmaceuticals and biological materials (51). Supercritical CO_2 has special properties which makes it an excellent environment for the formation of dry particles, such as ibuprofen, aceclofenac, diclofenac and other NSAIDs. One of these properties is the low solubility of most drug molecules in supercritical CO_2 which is considered as an advantage as well as a challenge.

Supercritical fluid processing techniques have been applied to the particle formation in drug formulation (43-48). The methods of fine particle formation using supercritical CO_2 are classified into several categories according to the role of supercritical CO_2 and the use of the second solvent. These include supercritical antisolvent (SAS), rapid expansion of supercritical solutions (RESS), and particles from gas-saturated solutions (PGSS). A significant disadvantage with nanoscale drug particles is the difficulty in their production. The physical instability of nanoscale particles to undergo aggregation is also a problem in the drug storage and administration (19-20).

1.4.2.1. Supercritical antisolvent process (SAS)

Supercritical antisolvent micronization has different acronyms, but the process is essentially the same in all cases; the differences are mainly related to the feed mode of solvent and antisolvent, being in co-current or countercurrent mode and to the kind of injector used. Nanoparticles are produced by droplet formation and the subsequent elimination of the solvent due to the fast mass transfer of CO_2 in the liquid. SAS process has been widely applied in many fields of research including pharmaceuticals, superconductors, coloring matters, explosives, polymers and biopolymers. This technique is also known as the aerosol solvent extraction system (ASES) or precipitation with a compressed antisolvent (PCA) process. A typical schematic diagram of SAS process is shown at Figure 3. Supercritical CO_2 is a relatively poor solvent for most polymers and pharmaceutical compounds. Co-solvents can be used to increase solubility of chemical compounds in CO_2. The micronization of polymers and biopolymers has been regarded as one of the earliest applications of the supercritical antisolvent technique. Micronization can be performed in batch or semi-continuous mode. Although the principle of the precipitation process is the same, batch and semi-continuous processes can produce totally different results in terms of morphology and particle size distributions of the processed material (58-59). Different particle morphologies have been produced such as nanometric and micrometric particles, amorphous particles or crystals. Reviews can be found in the literature that collect and comment on the results presented by the various authors (60).

The resulting particles are usually close to the spherical shape, since this shape is imposed on the droplets by the action of the surface tension, and it is maintained by the solid material that nucleates and grows within the boundaries of the original droplet. The diameter of the injector influences the distribution size of the droplets and, thus, the diameter of the particles (56). The majority of the supercritical anti-solvent studies have focussed on encapsulation of pharmaceuticals into biodegradable poly (esters) such as PLA and PLGA (57).

In this work supercritical antisolv method was used for the microencapsulation of ibuprofen into polyvinyl pyrrolidone. The produced microparticles were characterized using different analytical methods.

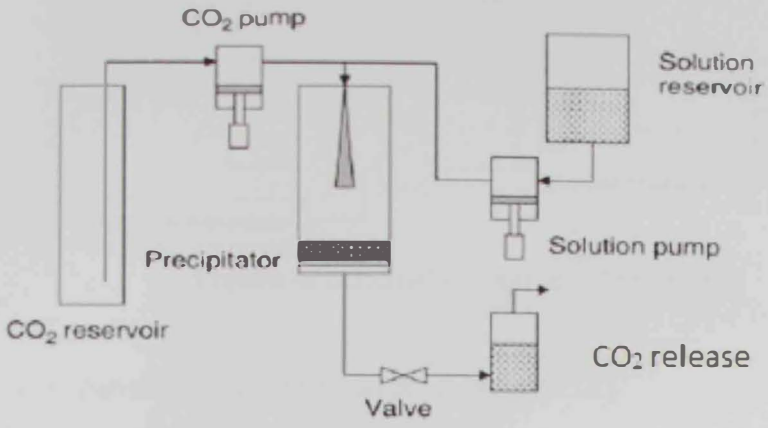


Figure 3. Schematic diagram of the SAS process

1.4.2.2. Solution enhanced dispersion by supercritical fluids (SEDS)

This process is a modified version of the SAS process in which the liquid solution and supercritical fluid are sprayed together using a specially designed coaxial nozzle. Two channel and three-channel nozzles are used for the precipitation of single and binary compounds, respectively. Supercritical fluid has a different role; it is used both as an antisolvent and as a dispersion medium. A high speed stream of solution carrying polymer, drug or any particle spontaneously contacts with the supercritical fluid. This generates the finely dispersed mixture and promptly achieves the target of particle precipitation. Adoption of three processing media, such as two different supercritical fluids and one organic solvent, can create more versatile operating variables. A typical schematic diagram of the SEDS process is shown in Figure 4.

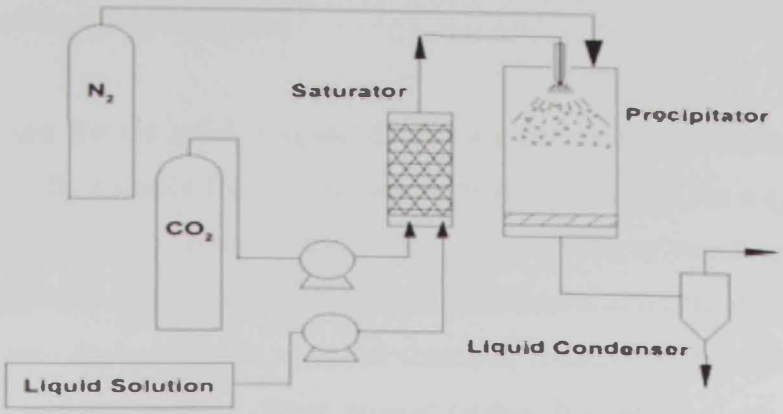


Figure 4. Schematic diagram of the SEDS

1.4.2.3. Rapid expansion of supercritical solutions (RESS)

This process is used when the polymer has some degree of solubility in supercritical fluids. A typical schematic diagram of the RESS process is shown in Figure 5. The pure drugs or drug-polymer mixtures are dissolved in a supercritical fluid and this high-pressure solution is rapidly depressurized through an orifice to lead to particle precipitation at a low pressure. Difference in solute solubilities in supercritical fluid at high and low pressure is the basic idea in this process. However, the main limiting factor is the low solubility of most pharmaceutical compounds and regulatory approved polymers in supercritical CO_2. To overcome this obstacle, co-solvents have been used to modify the polarity of the extracting phase and thus enhance solute solubility in the supercritical phase. Tom and Debenedetti (61) demonstrated that when 1% (w/w) acetone was used as a co-solvent, the solubility of PLLA increased by approximately 500%.

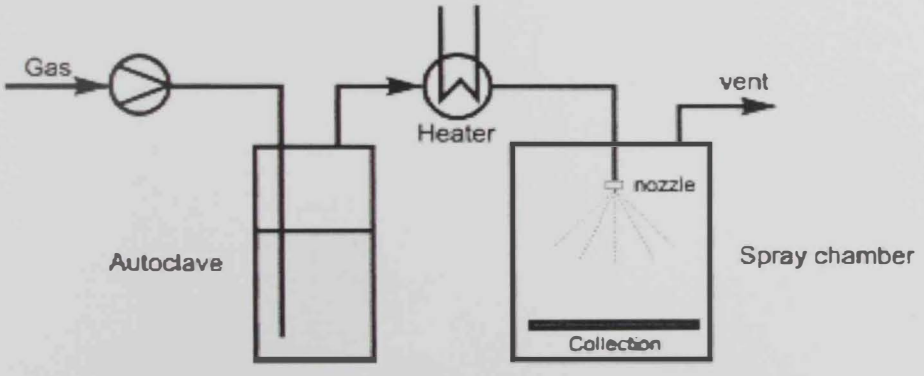


Figure 5. Schematic diagram of the RESS process

1.4.2.4. Gas antisolvent process (GAS)

This process is used for the solid compounds that are not soluble in supercritical fluid. The technique is especially suitable for drug-polymers mixtures because the majority of polymers are not soluble in supercritical fluids or gases. The drug-polymer mixtures are first dissolved in a liquid organic solvent, and a gas is employed as an antisolvent for the drug-polymer mixture by injecting gas into the solution in a closed chamber, resulting in precipitation of the solid particles. In this process there is direct proportionality between the gas concentrations in solution and the pressure. Usually SAS needs higher pressure than GAS (39). A typical schematic diagram of the GAS process is shown in Figure 6.

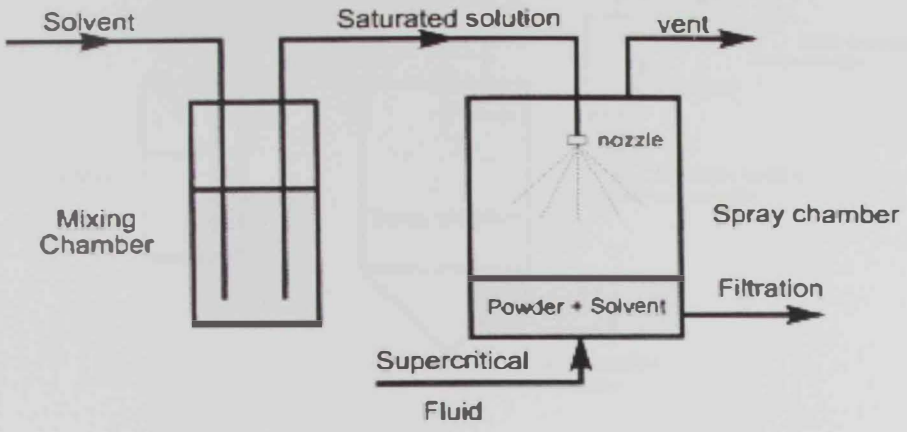


Figure 6. Schematic diagram of the GAS process

1.4.2.5. Particles from gas-saturated solutions (PGSS)

This process is designed for making particles of materials that absorb supercritical fluids at high concentrations until they get saturated. Even though the running industrial applications may currently be mostly on non-polymeric materials, the technique has great promise and is highly suitable for polymer powder production, particularly for powder coating applications. A typical schematic diagram of the PGSS process is shown in Figure 7.

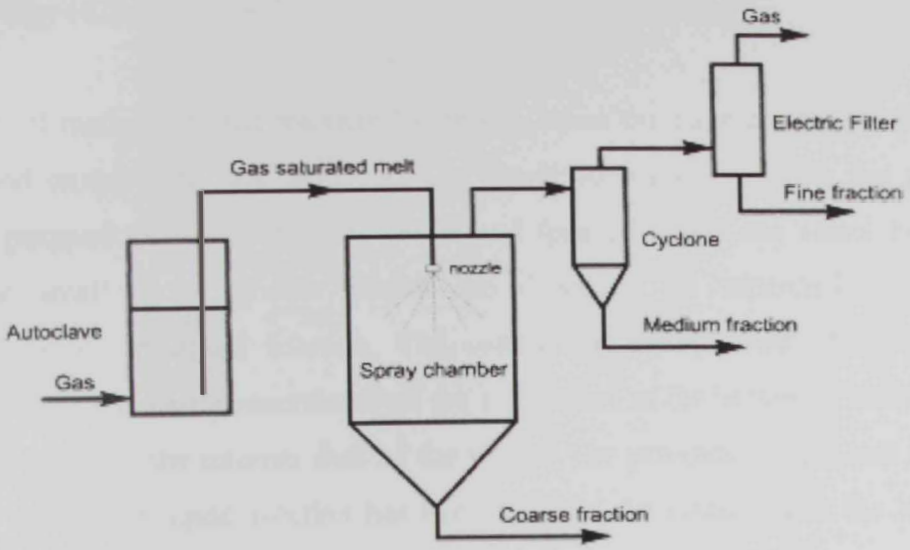


Figure 7. Schematic diagram of the PGSS process

1.4.3. Formation of polymer particles containing active ingredients using supercritical fluid technology

Supercritical fluid techniques have been widely used to produce a large variety of pharmaceutical compounds, and microparticles as shown in Table.1. The prepared microparticles were produced with controlled particle size and particle size distribution (PSD). Microparticles of nonsteroidal anti inflammatory drugs (NSAID's) such as ibuprofen (63), terbutaline (64), sulfamethizole (45) and insulin (46) are common products using supercritical fluid technology (62).

In the classical method of microparticle formation, when the supercritical conditions of CO_2 (pressure and temperature) are achieved, the liquid solution containing the drug and the polymer is pumped to the precipitator vessel and sprayed inside the vessel by means of a nozzle. The small drops of the solvent are dissolved by supercritical CO_2, causing supersaturation of the liquid solution. The consequent precipitation of the drug/polymer powder are formed and are accumulated on the frit located at the bottom of the vessel, as well as being deposited on the internal wall of the vessel. The precipitation process finishes when the desired amount of liquid solution has been fed into the system, then the liquid pump is turned off and the supercritical CO_2 continues to flow through the precipitator vessel to remove the residual content of the liquid solvent solubilized into the supercritical antisolvent (65).
It was found that higher polymer to drug ratios produced higher encapsulation efficiencies and the coated drug particles showed sustained release behavior (66).

Table 1. Literature review of different supercritical conditions used in microparticles formation

Author	P (bar)	T (°C)	Drug Solution (mg/ml)	Polymer (mg/ml)	Solution volume to CO_2 volume ratio	Flow rate (ml/min)	Specifications
A. Tenorio et al. (2007) (19)	150	40	20	5	1%	1	15:1 flow rate ratio CO2:sol.
Vega-Gonz´alez, A., e al. 2004 (20)	110	40	precipitation of polymer Only	2.8 wt% PLA in DCM*	6%	6	
Yulu Wang, et al, (2004) (21)	82	32	16	4	3%	0.7	The smaller the PS the more amount of polymer we have to use.
Joshua R. Bush, (2007) (22)	172	40	0.0287g drug/g polymer	0.1028g	10%	0.5	
Ana Rita C. Duarte, 2006 (69)	80	35	1.2g in 20ml ethanol	2g	3.2%	1	
Elisa Elizondo, 2010 (70)	100	35	-	100	5%	2	-Volume of CO2 30ml. -Spraying angle 60
Yulu Wang, 2006 (66)	89.6	33	5	5	1.5 standard liter/min SC CO2	0.8	
Amol J. Thote, Ram B. Gupta, 2005 (70)	103.42	40	10	80	5%	1	
M.A. Tavares Cardoso, 2008 (71)	130	50	57	-	-	-	Micronization is the objective

1.5. Thesis objectives

Osteoarthritis is a common disease affecting many people worldwide. Pain in the joints is the most common symptom of patients suffering from osteoarthritis. Ibuprofen, a nonsteroidal anti-inflammatory drug, is usually used as a pain killer for osteoarthritis patients. However low solubility of ibuprofen in the gastric fluid is a major limitation that affects the effecacy of this drug. Therefore, the main objective of this study was to enhance the aquous solubility of ibuprofen by forming drug-polymer microparticles. Supercritical fluid technology (supercritical CO_2) was used for encapsulating the ibuprofen drug into the polyvinylpyrrolidone (PVP) polymer. In particular, it was of our interest to use the supercritical antisolvent process (SAS) to form microcapsules. Different conditions (i.e. pressure, temperature, flow rates, and different drug solution:CO_2 volume ratios) were used in the preparation of the drug-polymer microparticles, and the solubility, dissolution rate and surface characteristics of the prepared drug-polymer microparticles were measured. Characterization techniques included fourier transform infrared spectroscopy (FTIR), ultraviolet spectroscopy (UV), transmission electron microscopy (TEM), scanning electron microscope (SEM), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

1.6. Outline of chapters

Chapter 2 discusses the experimental materials and methods used in this work including the experimental procedure, details of the apparatus, operating conditions used in preparing the microcapsules and the characterization methods. Chapter 3 includes the results and discussions. Results of the characterization methods are presented, analyzed and discussed. Finally, the conclusions are included in Chapter 4.

Chapter II
Materials and methods

Chapter II. Materials and methods

2.1. Materials

The non-steroidal anti-inflammatory drug (NSAID), used in this work was ibuprofen sodium salt of 91.0% minimum purity, which was purchased from Sigma–Aldrich Chemical. Ethanol (99.7% purity) and dichloromethane (99.7% purity) were supplied by VWR International Ltd, England. Methanol with a purity of 99.9% was supplied by Riedel-de Haen, Germany. CO_2 with purity higher than 99.8% was supplied by Sharjah Oxygen Co. Polyvinylpyrrolidone polymer with a molecular weight of 24,500 was generously supplied by the Chemistry Department at UAE University.

2.2. Methods

2.2.1. Formation of the microparticles

In the supercritical anti-solvent (SAS) process (Figure 8 and 9) the experiments began by delivering supercritical CO_2 at a constant flow rate to the precipitation chamber until the desired supercritical condition (pressure and temperature) of CO_2 were achieved. The liquid organic solution containing the drug and polymer was pumped to the precipitation vessel and sprayed inside the vessel by means of nozzles (either 0.075 micrometers or 0.15 micrometers diameters size). Precipitation of the solute was obtained and, when a given quantity of the solution was injected, the liquid pump was stopped. However, supercritical CO_2 continued to flow in order to wash the chamber, eliminating the organic liquid from the precipitate. At the end of the washing step, CO_2 flow was stopped, the precipitation chamber was depressurized down to atmospheric pressure and the sample was collected for analysis. After each run the lines were flushed with about 70 ml ethanol followed by 100 ml SC CO_2. The experimental conditions studied in this work are listed in Table 2.

Table 2. Experimental conditions for ibuprofen/PVP microparticle formation

Run #	Ibuprofen (g)	PVP (g)	Solvent volume (ml)	Temp. (°C)	Press. (bar)	Volume ratio (%)	Solution flow rate (ml/mi)	Observations	SEM Observations
1	0.500	0.125	25	40	150	1	1	No product	-
2	0.507	0.125	25	40	150	3	1	A lot of product.	Flakes and matrix of polymer.
3	0.5	0.125	25	40	150	4	1	A lot of product.	Agglomerated needles.
4	0.5	0.125	25	40	150	2	1	A lot of product	Needles network.
5	0.5	0.125	25	40	120	4	1	A lot of product	Needles and star shapes.
6	0.5	0.125	25	40	100	4	1	A lot of product	Big chunks of agglomerated stars
7	0.5	0.125	25	40	90	4	1	A lot of product	Big chunks
8	0.5	0.125	25	40	85	4	1	A lot of product	Big chunks
9	0.5	0.125	25	35	150	4	1	A lot of product	Agglomerated big chunks.
10	0.5	0.125	25	50	150	4	1	No product	-
11	0.5	0.125	25	50	150	4	1	A lot of product	Agglomerated stars
12	0.5	0.125	25	40	120	2	1	Only traces of product	No enough amoun for detection
13	0.5	0.125	25	40	120	6	1	A lot of product	Stars/ snowflakes.
14	0.5	0.125	25	35	120	4	1	Flow rate hardly controlled.	Stars /snowflakes.
15	0.5	0.125	25	50	120	4	1	A lot of product	Agglomerated needles.
16	0.5	0.125	25	40	120	2	1	A lot of product	Agglomerated small chunks.
17	0.5	0.125	25	40	120	4	1	A lot of product	Agglomerated big chunks.
18	0.5	0.125	25	40	120	4	0.5	A lot of product	Agglomerated big chunks.
19	0.5	0.125	25	40	110	4	1	A lot of product	Separated small beads of different shapes.
20	0.1	0.375	25	40	110	4	1	A lot of product	Agglomerated flakes.
21	0.1	0.375	25	40	110	6	1	Flow rate hardly controlled.	Melted polymer.
22	0.5	0.125	25	40	110	4	1	A lot of product	-
23	0.5	0.125	25	40	110	2	1	A lot of product	-
24	0.5	0.125	25	40	100	4	1	No product.	-
25	0.5g	0.125	25	40	150	1	1	*nozzle size 0.15μm. A lot of product	-

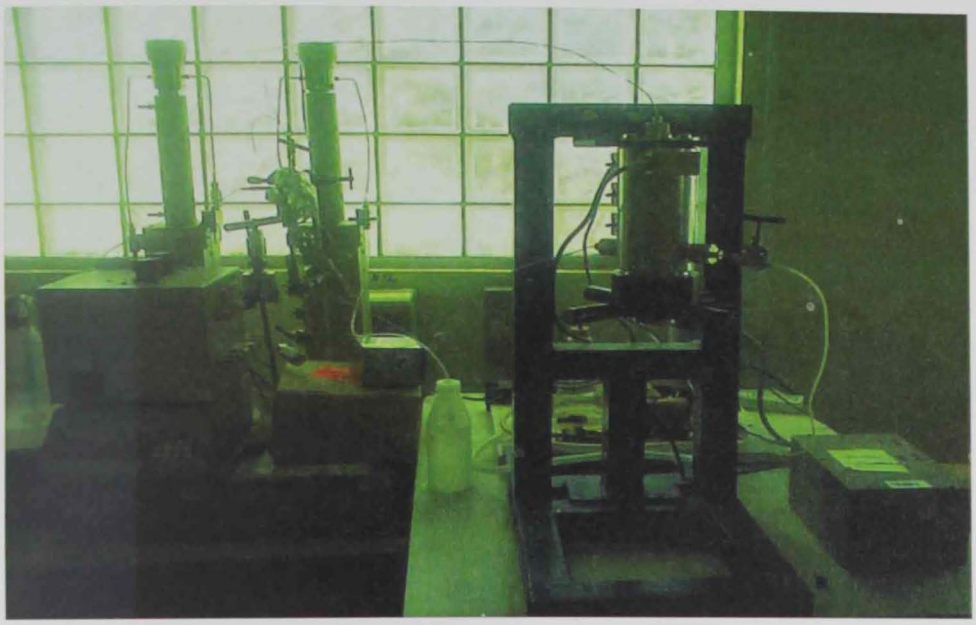


Figure 8. Photograph of the supercritical anti-solvent apparatus

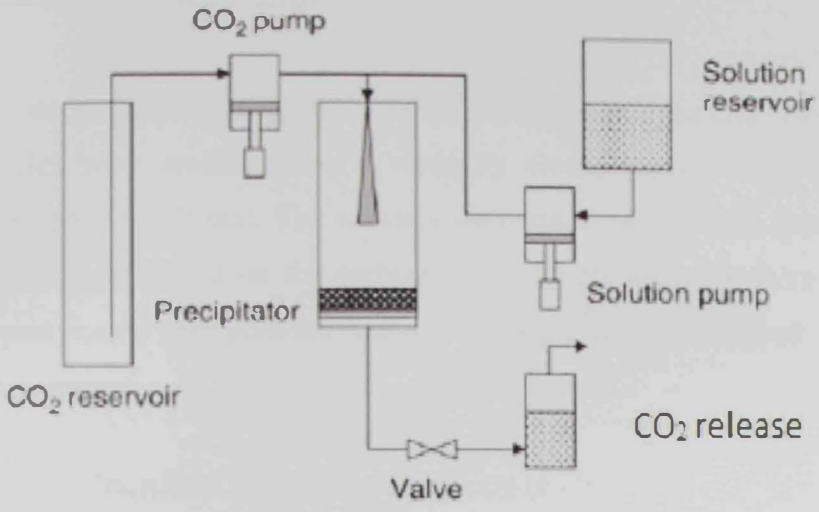


Figure 9. Schematic diagram of the SAS process

2.2.2. Characterization

2.2.2.1. Scanning Electron Microscopy (SEM)

The morphology and primary particle size of the neat polymers and neat drugs, PVP/Ibuprofen drug particles were studied using a scanning electron microscope (NeoScope JCM-5000 supplied by Jeol Ltd., Japan). The samples were prepared by direct deposition of the powders onto a carbon tape placed on the surface of an Aluminum stub. Prior to SEM analysis, the samples were coated with gold for 4 minutes using a sputter coater after which they were fed into the microscope.

2.2.2.2. Fourier Transform Infrared Spectroscopy (FTIR)

Transmission infrared spectra of all samples were recorded at room temperature using FT-IR (NEXUS-470, Thermo Nicolet Corporation) spectrophotometer in the range of wavenumber from 4000 to 400 cm^{-1} during 32 scans, with 2 cm^{-1} resolution. Granules of each sample were mixed in a ratio of 1.0 wt% with KBr powder dried at 120°C for 24 hours. The mixture was milled to a fine powder and placed in a mold under the hydraulic pressure to form a KBr disc. The sample disc was mounted directly onto the sample holder and data for the spectra was collected after scanning the background.

2.2.2.3. Transmission Electron Microscopy (TEM)

Transmission electron microscopy (TEM) is a microscopy technique whereby a beam of electrons is transmitted through an ultra thin specimen containing the sample stained by Urinyl acetate stain. By using a Phillips CM10 Transmittance Electron microscope, an electron beam was transmitted through a 200μm mesh cupper grid coated with carbon membrane and traces of the sample in milligrams were added to partially coat the grid. The samples were then contrasted by adding drops of 12% uranyl acetate stain for 3 minutes. The samples were injected into the TEM instrument, then as the electron beam passed through the specimen it

caused excitation followed by relaxation of the electrons of the sample and the images were formed from the interaction of the electrons transmitted through the specimen. The images were then magnified and focused onto a fluorescent screen. The images were printed on a layer of photographic film and the films were scanned into a computer.

2.2.2.4. Differential scanning calorimetry (DSC)

Differential scanning calorimetry or DSC is a thermoanalytical technique that measures the difference in the amount of heat required to increase the temperature of a sample and a reference, as a function of temperature. Both the sample and reference were maintained at nearly the same temperature throughout the experiment. The temperature program for a DSC analysis was designed such that the sample holder temperature increased linearly as a function of time.

Some amount of sample was transferred into a standard aluminum pan, weight was not important in this step since we were looking for the sample behavior. The sample holder was then covered with aluminum cover. The aluminum capsule was transferred into the DSC instrument programmed to run from 25°C to 600°C at 20°C/min heating rate and the exothermic or endothermic events related to crystallization or melting were recorded.

2.2.2.5. Thermogravimetric Analysis (TGA)

TGA is a test performed on the neat drug, neat polymer and the combination of the drug/polymer in the prepared microparticles that determines the changes in weight or weight loss in relation to changes in temperature. Such analysis relies on a high degree of precision in three measurements: weight, temperature, and temperature change. Analysis was carried out by raising the temperature of the sample gradually and plotting weight loss (percentage) against the temperature. A few milligrams of the sample were transferred into the aluminum pan and placed in the sample holder (sensitive electronic balance) inside the TGA instrument. The instrument was programmed to run from 25°C to 600°C at a heating rate of 20°C/min. After the data was obtained, curves were smoothed and points of inflection were detected.

2.2.2.6. Dissolution Rate

Dissolution rate of the drug was determined by the paddle stirring method at 37 ± 0.5 °C with the stirring speed of 100 rpm. Drug formulations equivalent to 100 mg of drug was applied in 500 ml of enzyme-free simulated gastric fluid (pH = 1.4 ± 0.1). Dissolution samples (1 ml) were collected at given time intervals with the replacement of equal volume of temperature-equilibrated media and filtered through 5 μm membrane filters. These samples were diluted to 10 ml with simulated gastric fluid and the drug dissolved was measured using an UV-Vis spectrophotometer at different time intervals 5, 10, 15, 20, 30, 45 and 60 minutes. The trials were repeated with higher time durations of up to 180 minutes.

Chapter III

Results and discussion

III. Results and discussion

One of the main objectives of this work was to characterize the neat ibuprofen, neat polyvinylpyrrolidone and the prepared microcapsules. In order to achieve this objective, six different characterization methods were used. Resulting images and graphs were analyzed in order to obtain the properties of the prepared microparticles such as their size, shape, order of the coating layers and thermal properties.

3.1. Scanning electron microscopy (SEM)

SEM study is a primary step in obtaining information about the surface area and morphology of the microcapsules. Magnification in a SEM can be controlled over a range of up to 6 orders of magnitude from about 10 to 500,000 times. Figures 10 to 16 show the various magnifications ranging between 5 to 200 microns. Figure10 shows ibuprofen drug particles, which consisted of irregularly shaped crystalline morphology with sharp edges, of around 100 microns lengths. Neat polyvinylpyrrolidone particles were regularly shaped spheres ranging from 10 to few hundreds of microns diameter as shown in Figure 11.

In general the temperature of the chamber in the SAS system (35°C- 50°C), has negligible effect on the morphology. Thus the temperature was kept constant at 40°C. Also, the concentration of the drug and polymer has been kept constant. At a high pressure of 150 bar (Figure 12-13 and 18), microcapsules were needle shape and the needles tended to agglomerate when the solution:CO_2 volume ratio was increased (Figure 12, 14, 15, 16 and17). When the temperature and the solution:CO_2 volume ratios were kept constant and the pressure was decreased, microcapsules had needle and star shapes at 120 bar (Figure 14). These star shape microparticles tended to agglomerate when the pressure was reduced and the microcapsules showed the shape of large chunks of stars at 90 bar (Figure 16) and 85 bar (Figure 17). This is due to the fact that the higher the pressure of the supercritical CO_2 the higher its density and solvent power, which lead to better solubility of drug and polymer in the supercritical CO_2. Processing the polymer with SC CO_2 does not leave residual organic solvent in the prepared drug/polymer microparticles since CO_2 is a gas under ambient conditions. Once the process

was complete and the system pressure was reduced, CO_2 left the sample, and separated microparticles with a relatively uniform particle size distribution were formed. Similar conclusions have been reported in previous works (73). At a constant pressure (150 bar) as the temperature was decreased from 40°C to 35°C, the microcapsules tended to have the shape of agglomerated chunks (Figure 18).

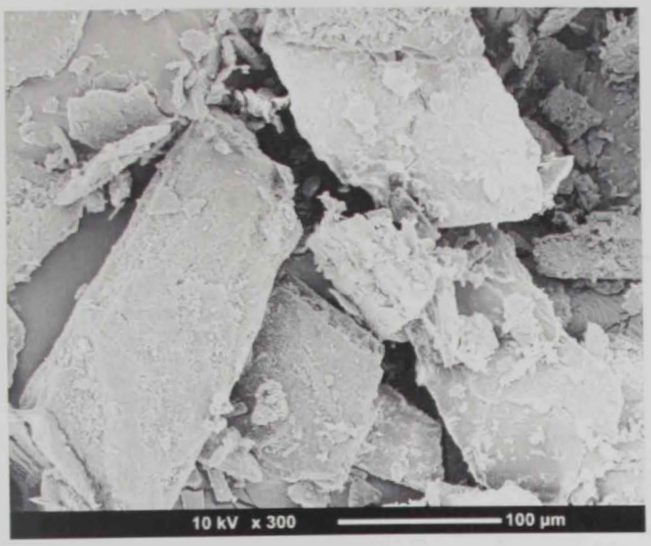


Figure 10. SEM images of the neat ibuprofen

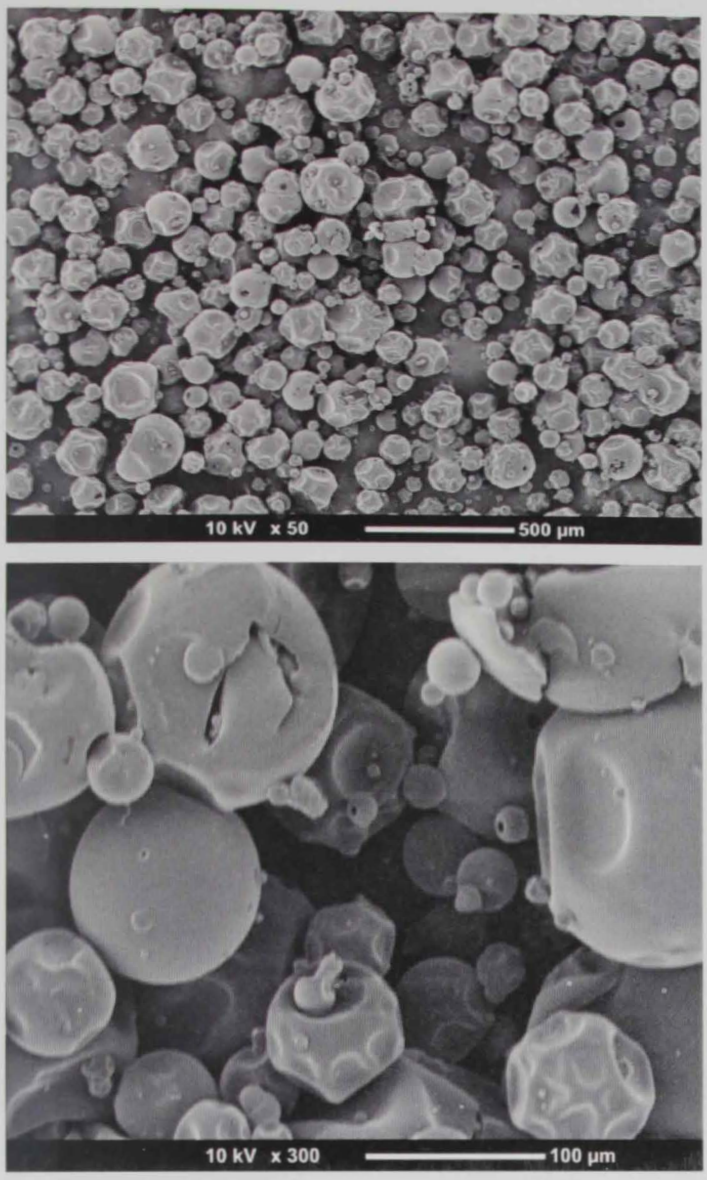


Figure 11. SEM images for the neat polyvinylpyrrolidone

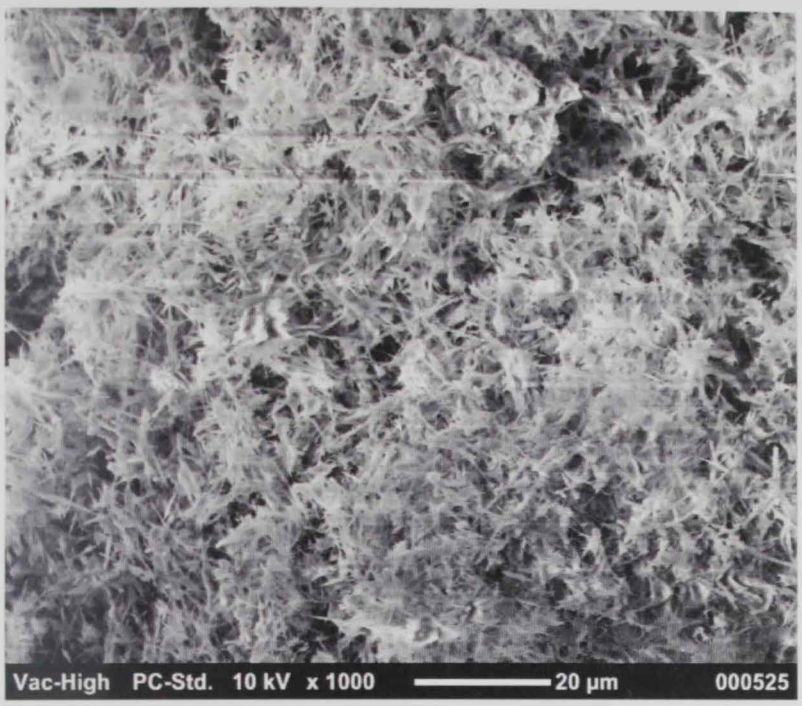


Figure 12. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 150 bar and 4% volume ratio

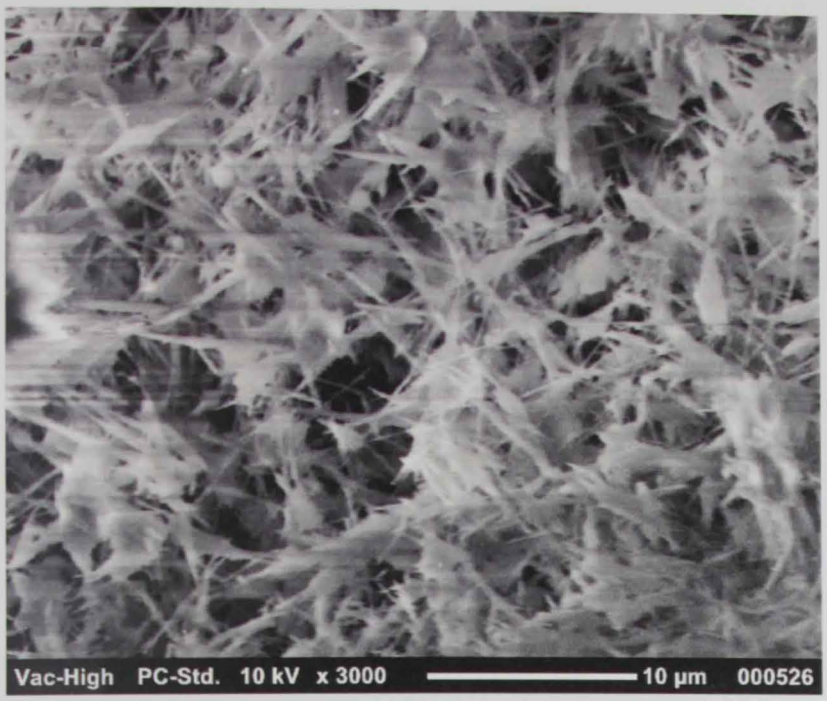


Figure 13. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 150 bar and 2% volume ratio

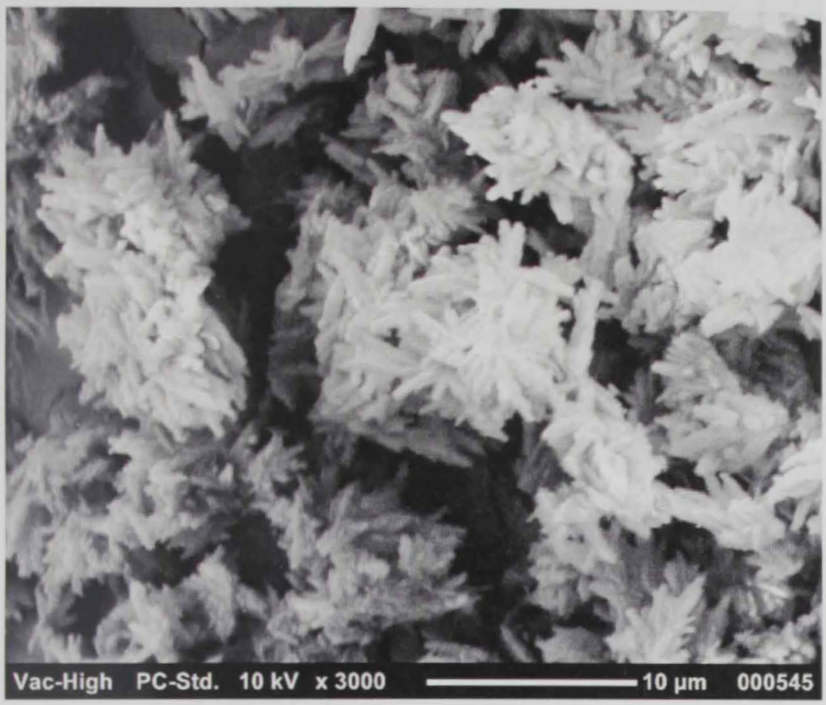


Figure 14. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 120 bar and 4% volume ratio

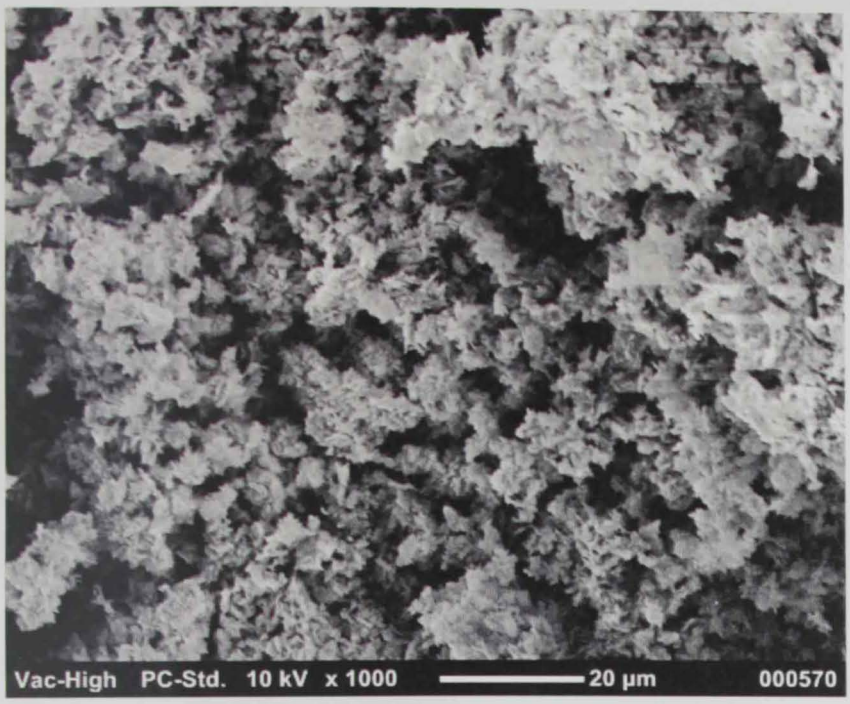


Figure 15. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 100 bar and 4% volume ratio

Figure 16. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 90 bar and 4% volume ratio

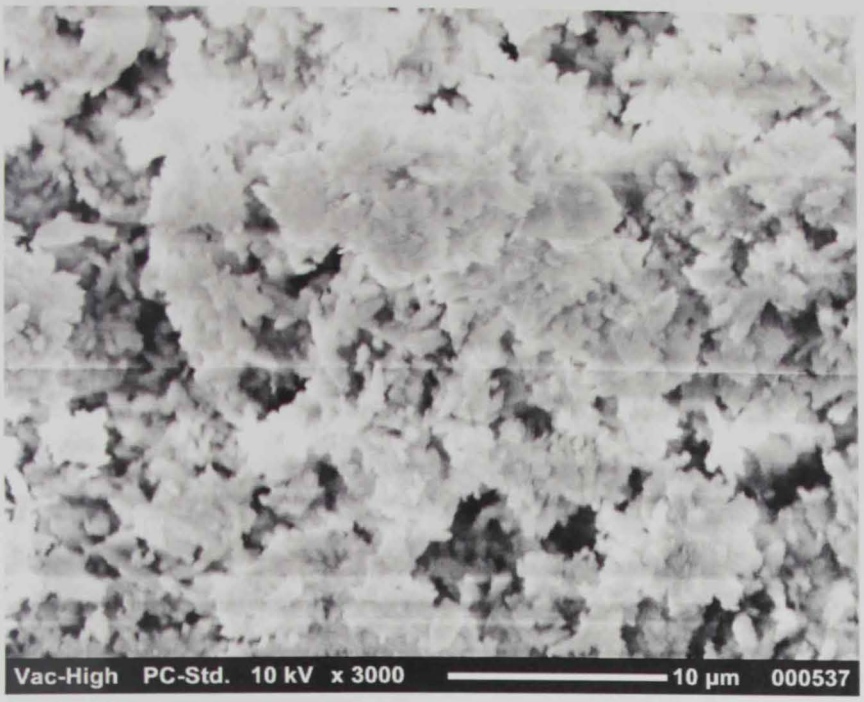


Figure 17. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 85 bar and 4% volume ratio

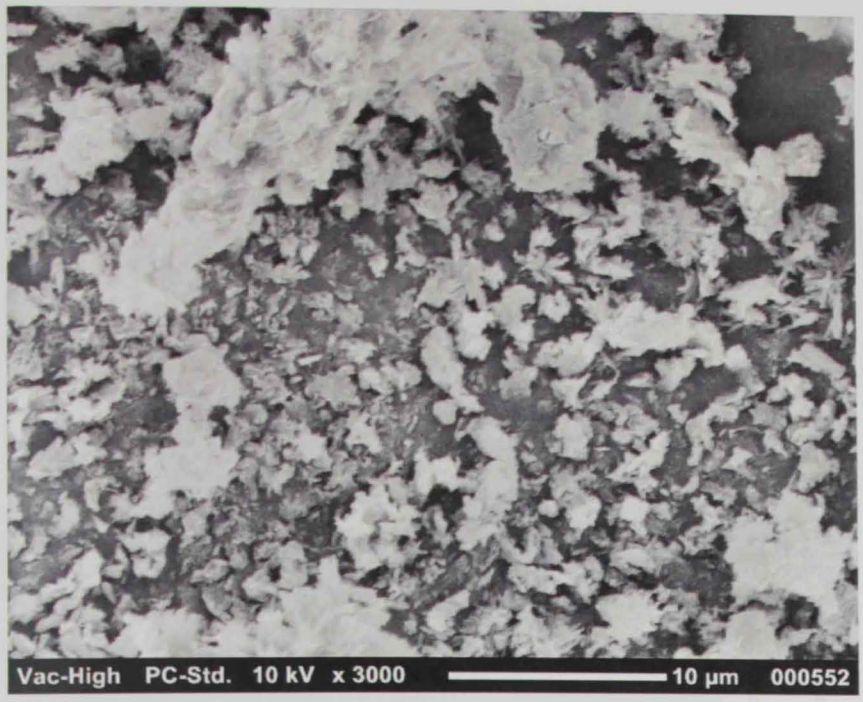


Figure 18. SEM images for the PVP/ ibuprofen microcapsule prepared at 35°C, 150 bar and 4% volume ratio

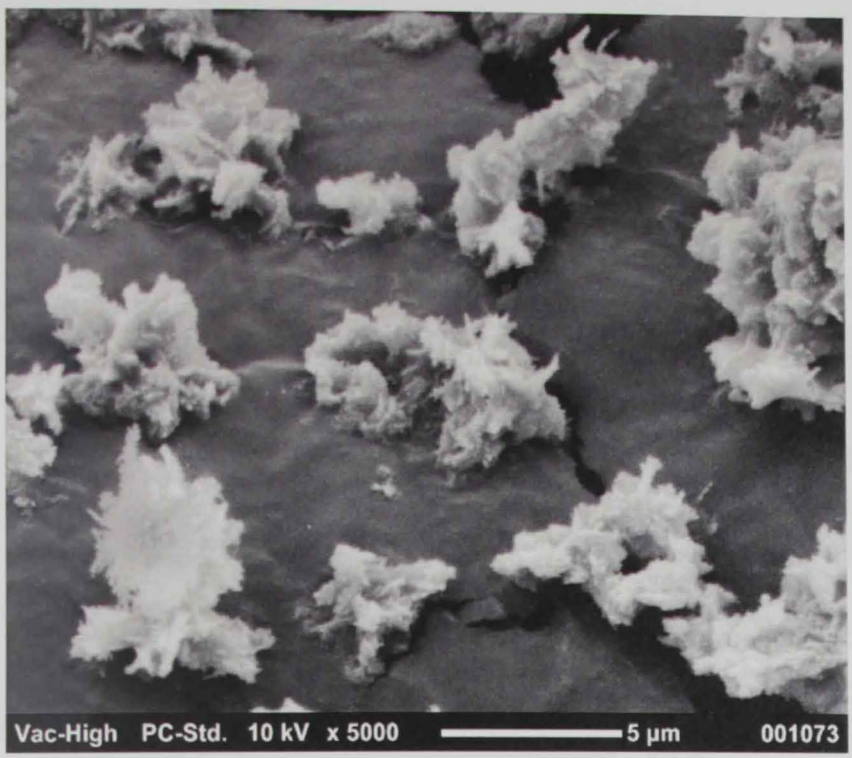


Figure 19. SEM images for the PVP/ ibuprofen microcapsule prepared at 40°C, 110 bar and 4% volume ratio

3.2. Fourier transform infrared spectroscopy (FTIR)

In the IR spectra the objective was to check the content of the microcapsules by studying the IR spectra for the neat ibuprofen, the neat PVP spectrum and then comparing them with the prepared microparticles spectrum. Neat polyvinylpyrrolidone spectrum had a broad band at 3440 cm^{-1} that was due to the stretching in the amine group N-H, then a medium band at 2925 cm^{-1} indicated the changes of relative absorbencies of the band at 2925 cm^{-1} (methylene groups of aliphatics). Due to the carbonyl C=O group stretching there was the sharpest band at 1662 cm^{-1}, and the rest of the noise bands were due to the aromatic C-H bending motion.

In the case of ibuprofen, FTIR spectrum showed broad band between 2800-3700 cm^{-1}, which is due to the carboxylic acid O-H stretching motion, another band in the range of 2500-3000 cm^{-1} was due to O-H stretching motion, overlapped with a broad small band due to alcohol O-H group stretching motion, at 3200-3550 cm^{-1}. At 1500-1700 cm^{-1} there are two medium bands due to the aromatic C=C bond bending. Then there was a medium band at 600-900 cm^{-1} which is due to the C-H bending and ring puckering. The C=O group of ibuprofen coated by PVP at 1727 cm^{-1} was shifted to a higher wavenumber region, compared to the neat ibuprofen spectrum at 1710 cm^{-1}. This indicated the breakage of the ibuprofen-ibuprofen interactions, which are characteristics of the solid form of this drug, once ibuprofen molecules were encapsulated into PVP using the SC CO_2.

As for the spectrum of microcapsules in (Figure 20a-f), all the samples of different pressures had the broad band due to the stretching of the N-H group, at 3440 cm^{-1}, similar to the PVP spectra and the ibuprofen spectra. Another notable change in the spectra was a decrease in the band to a value of 1636 cm^{-1}, which was a shif to the lower wavenumber compared to the neat PVP at 1652 cm^{-1}. This shift was due to the H-bond between the C=O of the carbonyl group in the PVP with the O-H group of the ibuprofen.

Another small band appeared in the microcapsules spectrum at 2920 cm^{-1}, due to the stretching motion of the carboxylic acid group, similar to the ibuprofen FTIR spectrum. Another indicator of the presence of the drug and the polymer in the microcapsule, appeared from the band at 1620 cm^{-1}, when comparing this band with the drug and the polymer spectrum, it was concluded that this band was an overlapping between C=O stretching band at 1662 cm^{-1} from the PVP spectrum, and the C=C stretching band at 1550 cm^{-1} from the ibuprofen spectrum.

A doublet peak appeared between 1550-1600 cm^{-1} in the spectrum c (100 bar), d (85 bar), e (120 bar) and f (110 bar), when the volume ratio was ranging between 2-4%. It can be concluded that not all the drug was encapsulated into PVP at lower pressures. The H-bond between ibuprofen and PVP had an effect on the interaction between PVP and CO_2. Evidence of this was shown from the split of the peak between 1550-1600 cm^{-1} in the FTIR spectrum, corresponding to the bending motion of CO_2, which is a strong indication of CO_2 interaction with the polymer. This is similar to what has been reported in earlier works (Kazarian et al., 1996) (74). However this splitting in the bending motion tended to disappear once ibuprofen was encapsulated into PVP, indicating that in such a case the CO_2 molecules did not interact with C=O group of PVP. There is always competitive interaction of ibuprofen and CO_2 molecules with C=O groups of PVP, however ibuprofen is interacting more strongly with C=O groups of PVP, and thus expels the CO_2 from the available interaction basic sites of C=O groups of PVP. There were some CO_2 that were still interacting with C=O groups of PVP, and this was shown by the fact that some distortion of the bending motion of CO_2 still existed after ibuprofen was encapsulated.

On the other hand at the higher pressure of 150 bar, which is presented at spectrum a (Figure 20), there was only a single peak at 1600 cm^{-1} due to the stretching motion of the C=O group in the PVP. A medium band appeared at 1330-1430 cm^{-1} due to O-H bending in-plane motion.

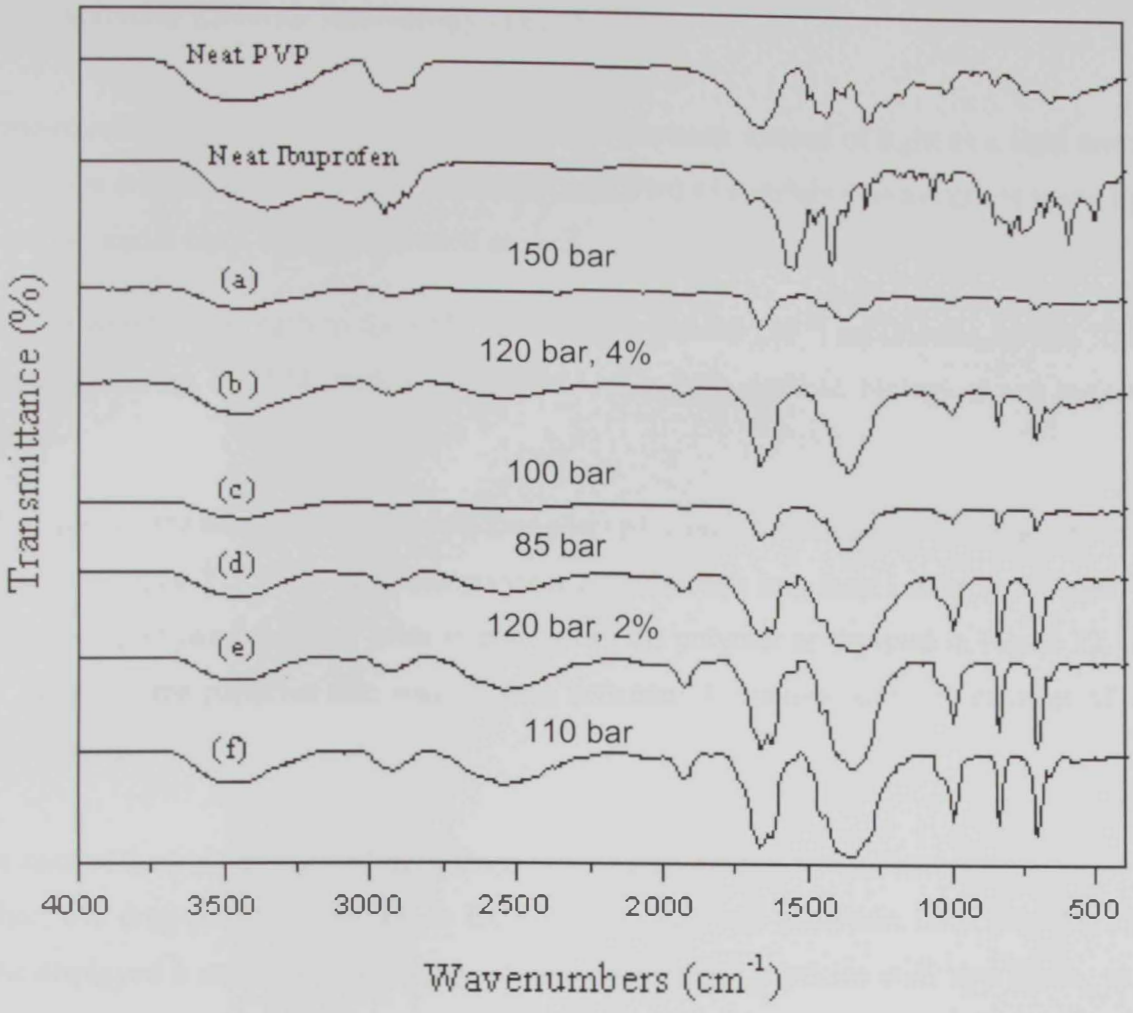


Figure 20. FTIR spectra for the neat polyvinylpyrrolidone, neat ibuprofen drug, (a) PVP/ ibuprofen microcapsule prepared at 150 bar and 40°C, (b) PVP/ ibuprofen microcapsule prepared at 40°C, 120 bar 4% volume ratio, (c) PVP/ ibuprofen microcapsule prepared at 40°C and 100 bar, (d) PVP/ ibuprofen microcapsule prepared at 40°C and 85 bar, (e) PVP/ ibuprofen microcapsule prepared at 40°C, 120 bar 2% volume ratio, (f) PVP/ ibuprofen microcapsule prepared at 110 bar and 40°C

3.3. Transmission Electron Microscopy (TEM)

The transmission electron microscope (TEM) uses electrons instead of light as a light source, which makes it applicable for various materials unlimited to a certain wavelength as in the light microscope, and it has a higher resolution as well.

TEM micrographs can reach to the order of a few angstroms (10^{-10} m) (atomic levels). These high magnifications of TEM made it a valuable tool in both medical, biological and materials research.

TEM images of the neat polyvinylpyrrolidone showed needle shape particles with a dark color as shown in Figure 21. The size of the polymer particles was less than 1 micron, whereas the ibuprofen drug showed a darker color in contrast to the polymer as depicted in Figure 22. The TEM image of the particles size was ranging between 10 microns and 100 microns of star shape particles.

In the case of the polyvinylpyrrolidone/ibuprofen microparticles, which were prepared at 35°C, 120 bar, 4% drug-polymer solution to CO_2 volume ratio and 1 ml/min flow rate, the TEM graphs displayed a uniform morphology of spherical shaped particles with two layers, as an indication of the drug layer and the polymer layer. The microparticle had the size of 0.1 micrometer diameter as shown in Figure 23. When temperature was increased by 15 degrees at 50°C, TEM images (Figure 24) showed the ibuprofen/ Polyvinylpyrrolidone microparticles of similar size to those observed in Figure 22 but the layers of the polymer and the drug were clearer. The lighter colour of the outer layer was an indicator of the polyvinylpyrrolidone layer and the darker colour of the inner layer was an indicator of the ibuprofen drug. Reducing the pressure in the preparation of the drug polymer microcapsule reduced the number of produced microspheres.

Staining the samples with uranyl acetate stain, enhanced the contrast of the resulting TEM image, and protected the samples from burning under the high energy radiation of the electron beam.

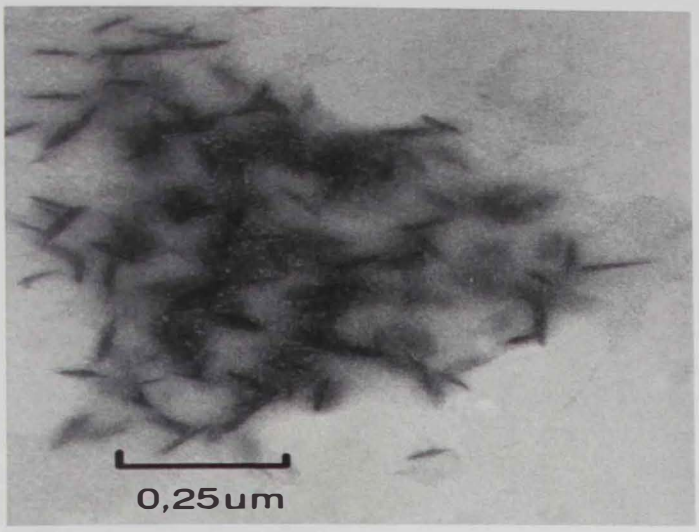


Figure 21. Transmission electron micrograph of the neat polyvinylpyrrolidone

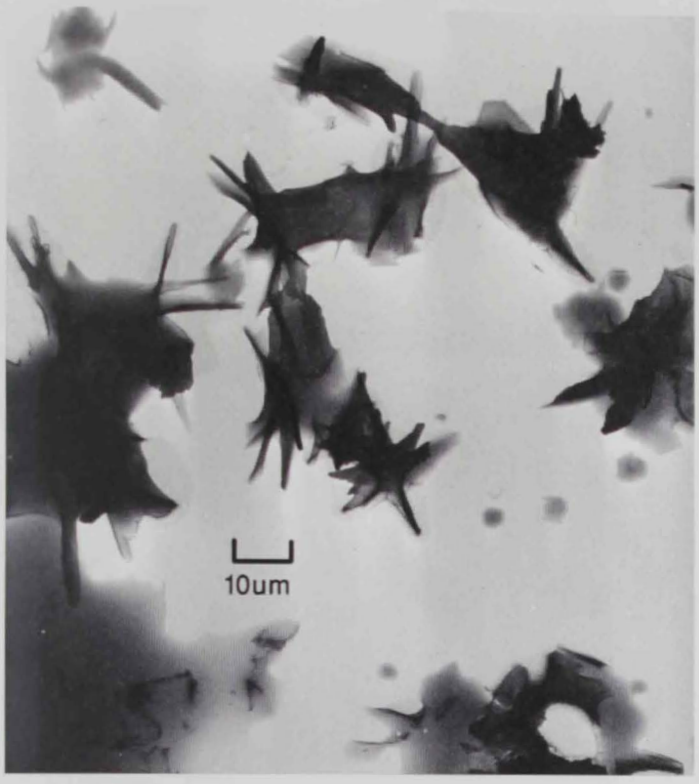


Figure 22. Transmission electron micrograph of the neat ibuprofen

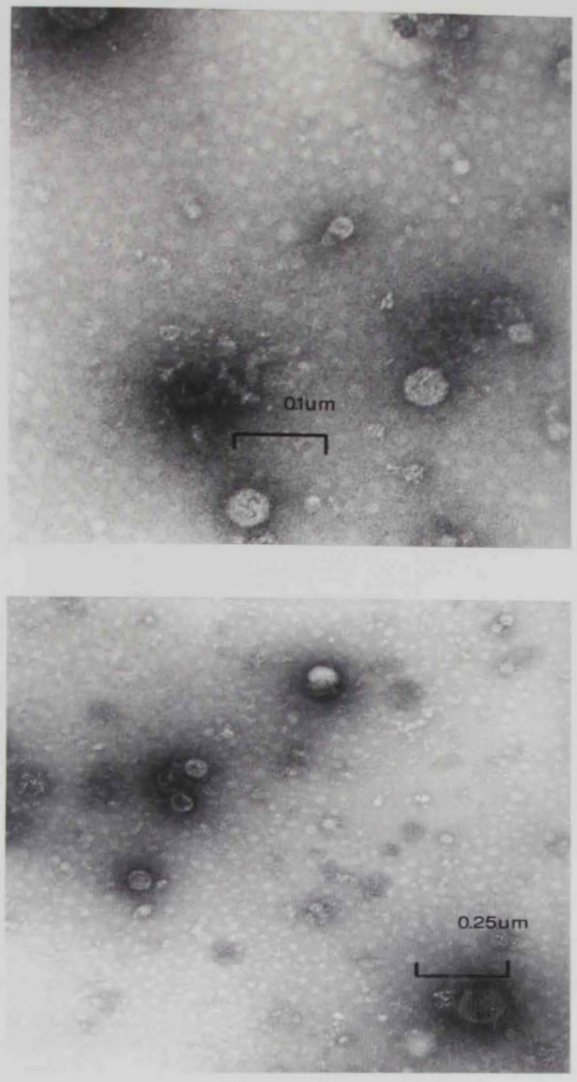


Figure 23. Transmission electron micrograph of the encapsulated PVP and ibuprofen drug at 35°C, 120bar, 4% volume ratio and 1 ml/min flow rate

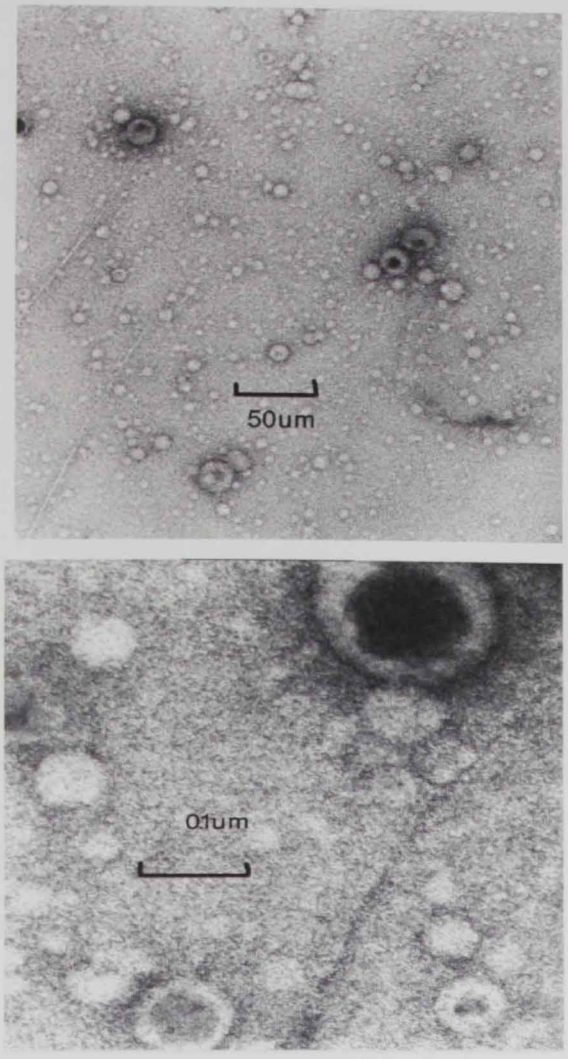


Figure 24. Transmission electron micrograph of the encapsulated PVP and ibuprofen drug at 50°C, 120 bar, 4% volume ratio and 1 ml/min flow rate

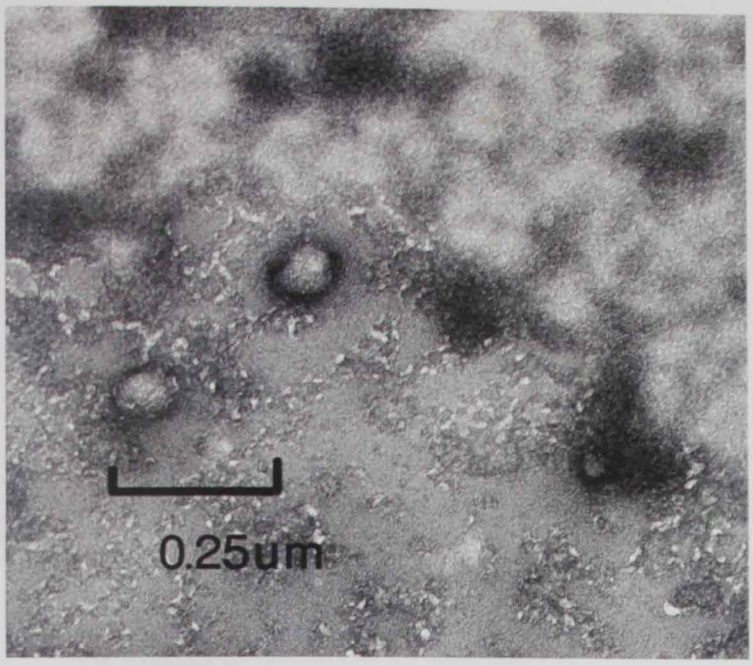


Figure 25. Transmission electron micrograph of the encapsulated PVP and ibuprofen drug at 40°C, 110 bar, 2% volume ratio and 1 ml/min flow rate

3.4 Differential scanning calorimetry (DSC)

DSC results of PVP polymer (Figure 26a) showed the glass transition temperature, which appeared as an endothermic peak at 175°C of the recorded DSC signal. This was due to the sample undergoing a change in the heat capacity, as the temperature of an amorphous solid was increased with no formal phase change. The cross-linking of the PVP molecules that may occur in the curing (hardening) process of the polymer is exothermic, resulted with a positive peak at 150°C in the DSC curve. This peak usually appears soon after the glass transition temperature. A negative peak was observed at 450°C due to melting of the PVP polymer.

DSC results for the ibuprofen drug shown in (Figure 26b), started with a sharp endothermic peak caused by the loss of moisture content in the drug, due to the constant heating. A following exothermic peak appeared at 100°C, due to the exothermic crystallization process. It is desirable to process the drug at temperatures below those at which crystallization can occur if it should be delivered in amorphous phase.

DSC results of the PVP/ibuprofen microcapsules (Figure 26c) showed the first endothermic peak due to the glass transition of the polymer. This peak also corresponds to the moisture loss in the ibuprofen drug. Neat PVP had a narrower and a sharper peak in comparison with the conditioned PVP/ibuprofen microparticles.

In the DSC results, the endothermic peak corresponding to the net ibuprofen was also observed for the prepared PVP/ibuprofen microparticles using SC CO_2, indicating an incomplete inclusion of the drug in PVP. This agreed with the TEM results when the ibuprofen was the shell and the PVP was the core of the microparticles. The exothermic crystallization process occurred at 300°C, which was slightly shifted from the crystallization peak of the drug and the polymer.

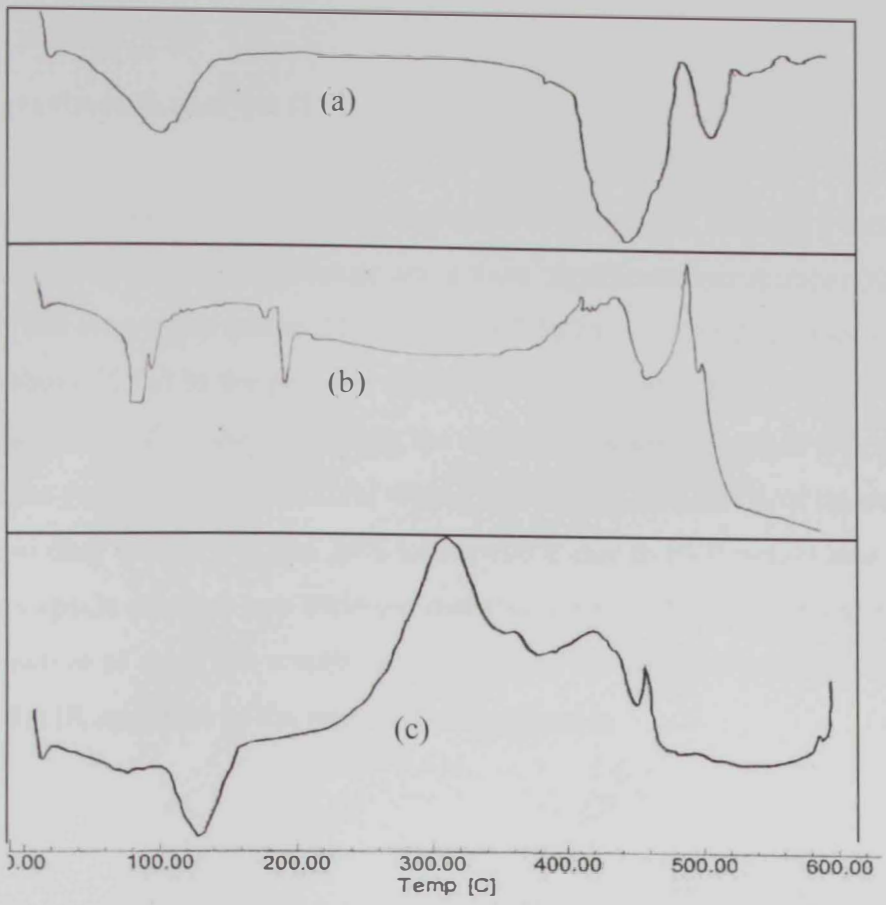


Figure 26. Differential scanning calorimetry curve (a) for the neat PVP, (b)neat ibuprofen and (c) microcapsule prepared by supercritical CO_2 technique at 40°C, 150 bar, 4% volume ratio and 1ml/min flow rate.

3.5 Thermogravimetric analysis (TGA)

The TGA diagram obtained for the neat ibuprofen (Figure 27a), showed a small decrease at around 100°C, due to the loss of moisture and a more significant loss at about 300°C. The PVP polymer also lost its weight (about 12%) at around 100°C (Figure 27b). However, the major weight loss (about 70 %) in the polymer occurred at around 400 °C. The TGA diagram of the microparticles (Figure 27c) showed clearly the different regions of weight loss associated with the drug and the polymer. This was clear where the capsule lost 22.4% of its weight at 300°C, which is due to drug weight loss and 24% loss at 400°C due to PVP weight loss. This indicates that the microcapsule contains two different materials namely the ibuprofen and the PVP. And it is a confirmation of the FTIR results, which showed the different peaks of the PVP and the ibuprofen in the IR spectrum of the prepared microcapsules.

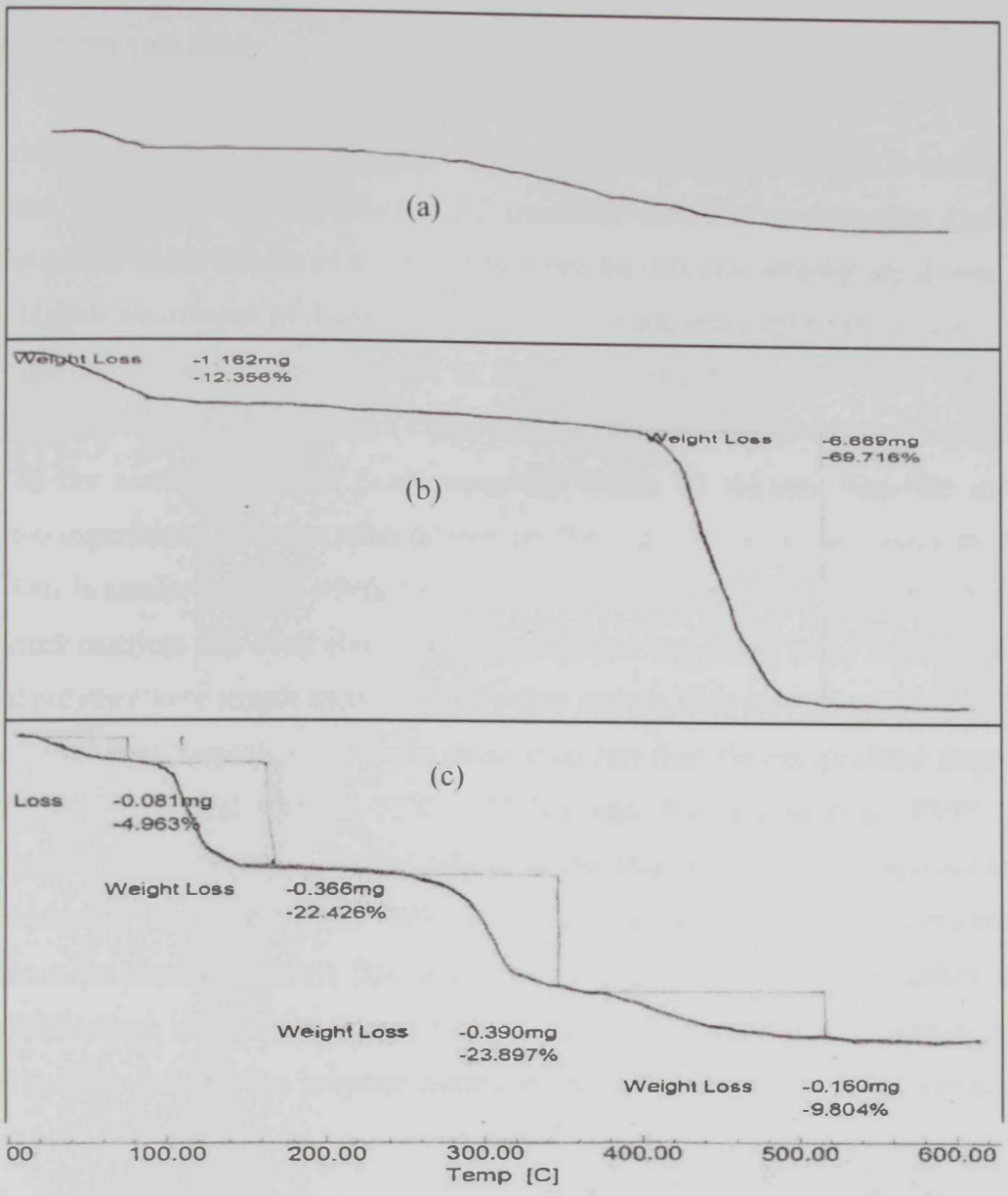


Figure 27. Thermogravimetric analysis for the (a) neat ibuprofen, (b) the neat polyvinylpyrrolidone and (c) the microcapsule prepared by supercritical CO_2 technique at 40°C, 150 bar, 4% volume ratio and 1 ml/min flow rate

3.6. Dissolution rate study

Dissolution profiles of samples prepared at different treatment pressures and temperatures were determined, in order to see the effect of SC treatment condition on ibuprofen dissolution in simulated gastric fluid. Results of the dissolution rate for different samples are shown in Figure 28. The highest absorbance of ibuprofem in the UV-Visible spectrophotometer was at 265 nm. PVP/ ibuprofen microparticles prepared at 35°C, 120 bar, 4% volume ratio and 1 ml/min showed the highest dissolution rate (Figure 28), where the drug in the beginning dissolved rapidly in the simulated gastric fluid, especially before 60 minutes from the start of the dissolution experiment, however, after 60 minutes the drug concentration dropped to around 50 µg/ml. This is similar to what others have concluded in the literature. Ibuprofen that is inside the polymer matrices has been shown to be amorphous and easier to be released than if the drug and polymer were simple mixtures where they exist in their crystalline forms (75). On the other hand the neat ibuprofen had lower dissolution rate than the encapsulated ibuprofen into PVP, using supercritical CO_2 at 35°C, 120 bar and 4% volume ratio. PVP/ ibuprofen microcapsules showed more controlled release of the drug from the microparticles when they were prepared at higher temperate (40°C and 50°C). In these samples, the concentrations of ibuprofen in the simulated gastric fluid were about 15 µg/ml, and remained constant, indicating a controlled release of the drug from the microparticles. This controlled release of the drug is because in these samples the polymer coated the drug, confirming the TEM images of these samples.

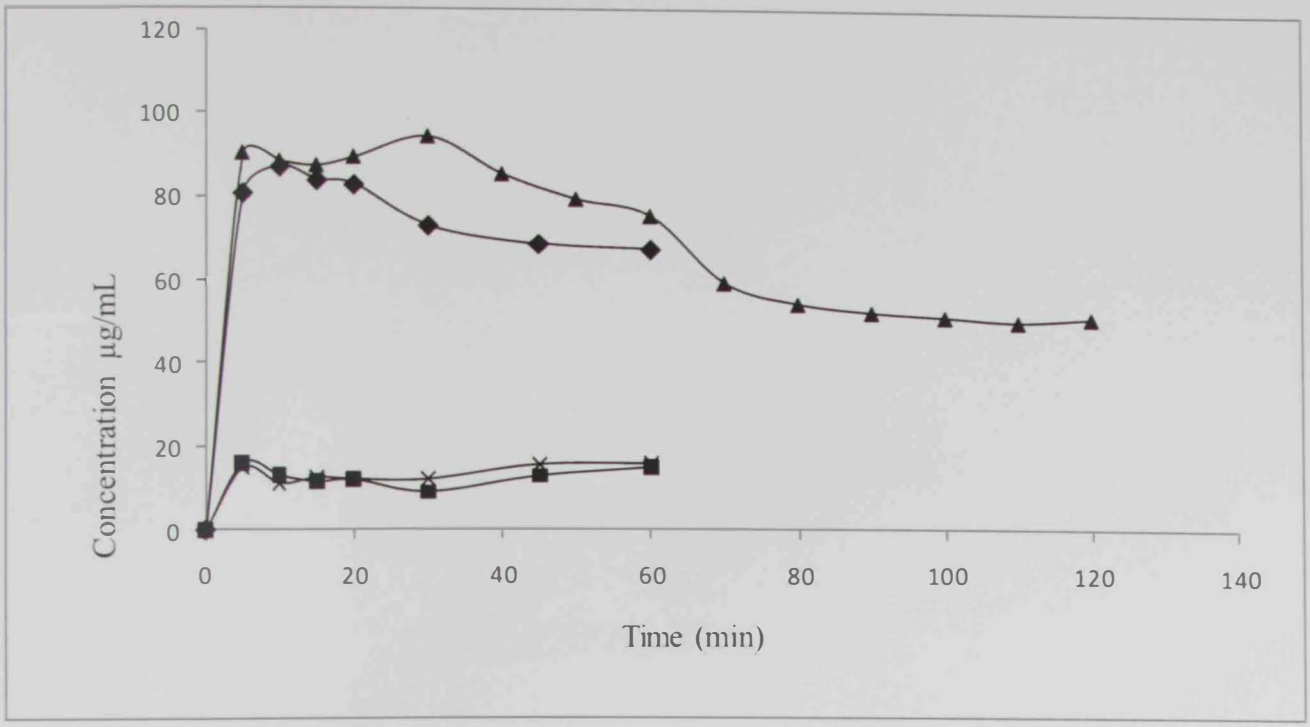


Figure 28. Dissolution rate for (♦) Pure Ibuprofen, (▲) PVP/ibuprofen microcapsules prepared at 35°C, 120 bar, 4% volume ratio, 1 ml/min, (■) PVP/ibuprofen microcapsules prepared at 40°C, 110 bar, 4% volume ratio, 1 ml/min flow rate, (×) PVP/ibuprofen microcapsules prepared at 50°C, 120 bar, 4% volume ratio, 1 ml/min flow rate.

Chapter IV

Conclusions

Chapter IV. Conclusions

From the SEM results it can be concluded that the higher pressure (e.g. 120 or 150 bar) gave more separated microparticles and smaller particle sizes (e.g. small chunks of 10 microns). Microparticles that were prepared at lower pressures (e.g. 90 or 85 bar) were bigger in size showing agglomerated chunks. This might have been caused by the presence of the organic solvent in the sample while at the higher pressure, supercritical CO_2 could remove the organic solvent due to the higher solubility of the solvent in supercritical CO_2 at the higher pressures.. This was confirmed from the doublet peaks of the FTIR test for the microcapsules, which were prepared at lower pressures (i.e. 85 bar, 100 bar).

Similarly, the higher the flow rate, the higher the presence of the organic solvent (ethanol) in the prepared drug-polymer microparticles. SEM results showed the agglomeration of the microparticles prepared at higher flow rates. Shorter contact time between the drug-polymer solution and supercritical CO_2 at higher flow rates prevents the supercritical CO_2 from removing all the organic solvent from the drug-polymer solution. Therefore, lower flow rates (1 ml/min) and thus higher contact times resulted in well separated micrparticles.

FTIR results clearly showed the presence of the PVP polymer and the ibuprofen in the drug-polymer microparticle samples, which was the first goal of the work. TGA results confirmed the fact that both PVP and ibuprofen molecules were present in the prepared microcapsule samples. TEM results confirmed that PVP polymer/ibuprofen microparticles were prepared and the ibuprofen was encapsulated into the PVP polymer. TEM results also showed that the prepared microcapsules were of small sizes that could reach 0.1 microns in diameter.

Finally, the dissolution rate of the ibuprofen from the drug-polymer microparticles prepared at the low temperature of 35°C showed a slight increase in comparision with the neat ibuprofen drug, indicating an enhancement of the solubility of the ibuprofen drug in the gastric fluid after the encapsulation into PVP polymer. On the other hand, a more controlled release was noticed from the microparticles which were prepared at high temperatures (40°C and 50°C), which might be due to the thicker polymer layer covering the drug at these temperatures.

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رسالة مقدمة من الطالبة

صفاء محمد المهدي علي يوسف

إلى

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استكمالا لمتطلبات الحصول على درجة الماجستير

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