

Microencapsulation of Ibuprofen into Polyvinylpyrrolidone Using Supercritical Fluid Technology

Safaa M Yousif¹, Ali H Al-Marzouqi² and Mahmoud A Mohsin^{3*}

¹Department of Applied Mathematics and Sciences, Khalifa University of Science, Technology and Research, Abu Dhabi, United Arab Emirates

²Department of Chemical and Petroleum Engineering, United Arab Emirates University, PO Box 15551, Al-Ain, United Arab Emirates

³Department of Chemistry, University of Sharjah, PO Box 27272, Sharjah, United Arab Emirates

Abstract

Osteoarthritis is a disease that attacks human bones especially in older people and usually non-steroidal anti-inflammatory drugs are being prescribed for patients with Osteoarthritis. These kinds of drugs usually have low aqueous solubility, dissolution and bioavailability. In order to maximize their therapeutic effects, these properties should be developed and enhanced. The purpose of this study was to reduce the particle size of ibuprofen by forming microparticles and thus enhance its dissolution rate. Ibuprofen was encapsulated into a polymer (polyvinylpyrrolidone) using supercritical fluid technology (supercritical CO₂) to form drug-polymer microparticles. Dissolution rate and surface characteristics of the prepared drug-polymer microparticles were measured 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 the operating conditions (i.e., different temperatures, pressures, flow rates and different drug solution:CO₂ volume ratio). Results from TEM images and FTIR graphs showed that microparticles were successfully prepared. Different conditions gave different morphologies of drug-polymer microparticles as was confirmed using SEM analysis. Finally, dissolution rate of the drug-polymer microparticles in a simulated gastric fluid showed a promising result and better drug release control over extended period of two hours in comparison with unencapsulated Ibuprofen.

Keywords: Microencapsulation; Ibuprofen; Polyvinylpyrrolidone; Supercritical CO₂

Introduction

Osteoarthritis (OA) is a common disease affecting many people worldwide. 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) [1]. Non-steroidal anti-inflammatory drugs in general are poorly soluble in water [2] and they are commonly administered orally causing gastrointestinal side effects such as gastric ulceration, perforation and sometimes bleeding [3,4]. The use of NSAIDs is associated with an increased risk of symptomatic pulmonary embolism [5], it might also be associated with an increased risk of vascular events [6]. Ibuprofen is a common NSAID used for the relief of symptoms of arthritis, fever [7] and also as an analgesic agent for pain, especially where there is an inflammatory component. However, ibuprofen is poorly soluble in water and has a short biological half-life of 2 hrs, which means that frequent doses are required to maintain the therapeutic efficiency over longer time. Previous studies results indicated that high dose ibuprofen (800 mg three times daily) was associated with an increased risk of vascular events [8] These problems can be solved by encapsulating the drug with a water soluble polymer forming microencapsulations which contain the drug as a core material in a physically bound state with the polymer backbone or to a side group. In this system, the drug is delivered by chemically or biologically induced cleavage of the hydrogen bond to achieve a more constant release of the drug for longer period of time thus decreasing the required dose, and the toxicity of the drug, making its solubility and therapeutic efficiency much improved and easily controlled.

Various techniques have been developed to improve the solubility of NSAIDs, including micronization, surfactant-aid dispersion, the use of organic solvents, emulsions and microemulsions, solid dispersion technology and carriers based on polymers and liposomes [9-13]. 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 [14-17]. 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 [18]. 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 [19]. 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. Interest in supercritical fluids (SCFs) and their

*Corresponding author: Mahmoud A Mohsin, Department of Chemistry, University of Sharjah, PO Box 27272, Sharjah, United Arab Emirates, Tel: 97165585000; E-mail: mmohsin@sharjah.ac.ae

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potential use for particle formation in drug formulation [20-24] has significantly increased in the past decade. The methods of fine particle formation using supercritical CO₂ are classified into several categories according to the role of supercritical CO₂ 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. In this work supercritical antisolvent method was used for the microencapsulation of Ibuprofen into polyvinyl pyrrolidone (PVP), which is a water-soluble polymer. The solubility of Ibuprofen extends from the extremely hydrophilic solvents such as water to hydrophobic liquids such as butanol.

Carbon Dioxide (CO₂) is the most commonly used fluid in supercritical fluid technologies. Some of the advantages of supercritical CO₂ are its mild operation condition (critical temperature and pressure of 31°C and 7.38 MPa, respectively), gaseous standard state under ambient conditions, nontoxicity and its relatively low cost compared to organic solvents. The aim of this research was to reduce the particle size of ibuprofen by forming microparticles and thus enhance its dissolution rate. At the same time, using water soluble polymer to encapsulate the drug with various thicknesses in order to control the release of Ibuprofen during the dissolution process. Ibuprofen was encapsulated into a polymer (polyvinylpyrrolidone) using supercritical fluid technology (supercritical CO₂) to form drug-polymer microparticles. Different conditions (i.e., pressure, temperature, flow rates, and different drug solution/CO₂ volume ratios) were used in the preparation of the drug-polymer microparticles. Dissolution rate and the chemical and physical characterization of the prepared drug-polymer microparticles were carried out using fourier transform infrared spectroscopy (FTIR), ultraviolet spectroscopy (UV), transmission electron microscopy (TEM), scanning electron microscope (SEM), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

Experimental Procedure

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. CO₂ 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.

Methods

Formation of the microparticles: Supercritical anti-solvent (SAS) process was used to form the microparticles (Figure 1). The experimental apparatus consisted of two 260 ml capacity syringe pumps and controller system (ISCO 260D, USA), a precipitation unit and a separation vessels. Temperature and pressure within the vessels were measured and could be independently adjusted. The experiments began by delivering supercritical CO₂ at a constant flow rate to the precipitation chamber until the desired supercritical condition (pressure and temperature) of CO₂ 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 CO₂ continued to flow in order to wash the chamber, eliminating the organic liquid from the precipitate. At the end of the washing step, CO₂ 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 CO₂.

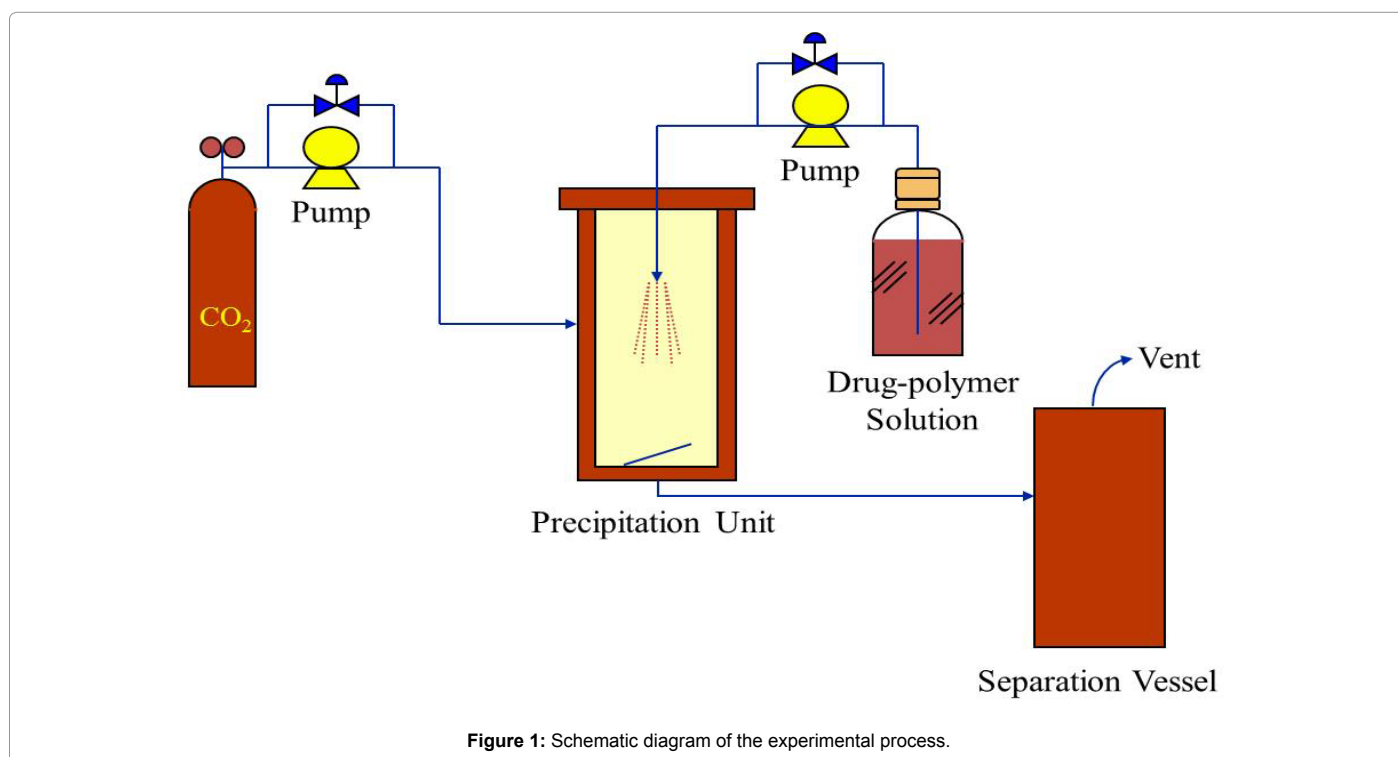


Figure 1: Schematic diagram of the experimental process.

Characterization

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.

Fourier Transform Infrared Spectroscopy (FTIR): Transmission infrared spectra of all samples were recorded at room temperature using FTIR (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.

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 Uranyl acetate stain. By using a Phillips CM10 Transmittance Electron microscope, an electron beam was transmitted through a 200 μm mesh copper 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.

Differential scanning calorimetry (DSC): A differential scanning calorimeter (DSC) (TA Instruments, Water LLC model Q200) containing a cooling system was used to examine the transition temperature (T_g) and melting temperature (T_m) for different samples. Each sample of weight around 5 mg was placed inside a hermetically sealed aluminum pan and heated with a constant heating rate of 10°C/min from 25°C to 600°C under nitrogen atmosphere. An empty hermetically sealed aluminum pan was used as a reference cell. The results were analyzed using the TA Universal Analysis 2000 V 4.5 A software. The glass transition temperature was determined where a base line inflection occurred, and the crystallization melting range or decomposition melting temperature was determined as the peak temperature of endothermic event of the DSC curves.

Thermogravimetric Analysis (TGA): TGA analysis of the drug and polymer-drug microparticles were performed using Thermogravimetric Analyzer TGA Q50 V20.10 Build 36 Model (TA Instruments, Water LLC) containing a TGA heat exchanger system. The samples (~10 mg each) were weighted in a pan and placed inside a tube furnace, which was heated to 600°C at a rate of 20°C/min under nitrogen atmosphere. The results were analyzed using the TA Universal Analysis 2000 V 4.5 A Build 4.5.05 (TA Instruments, Wilmington, Delaware, US) software.

Dissolution rate: Dissolution rate of the drug was determined by the paddle stirring method at $37 \pm 0.5^\circ\text{C}$ 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 ($\text{pH}=1.4 \pm 0.1$). 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.

Results and Discussion

Scanning Electron Microscopy (SEM)

Figure 2 shows SEM images of the pure Ibuprofen, pure polymer and drug/polymer microparticles. Ibuprofen drug particles consisted of irregularly shaped crystalline morphology with sharp edges, of around 100 microns lengths. When combined with polyvinylpyrrolidone the particles were regularly shaped spheres ranging from 10 to few hundreds of microns diameter. In general the temperature of the chamber in the SAS system (35°C- 50°C), had negligible effect on the morphology of the microparticles thus the temperature was kept constant at 40°C. Also, the concentration of the drug and polymer has been kept constant. At high pressure of 150 bar, microcapsules were needle shape, and the needles tended to agglomerate when the solution/ CO_2 volume ratio was increased. When the temperature and the solution/ CO_2 volume ratios were kept constant and the pressure was decreased to 120 bar the microcapsules had spheres shapes as shown in Figure 2. The microparticles tended to agglomerate when the pressure was reduced, and the microcapsules showed large chunks of stars at 90 and 85 bar. This may be 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 distribution of drug and polymer in the supercritical CO_2 . One of the major advantages of this technique, is that when processing the polymer/drug to produce microparticles, the CO_2 used does not leave residual organic solvent in the prepared drug/polymer microparticles since CO_2 is a gas under ambient conditions. Once the process is complete and the system pressure is reduced, CO_2 leaves the product, and separated microparticles with a relatively uniform particle size distribution are formed.

Fourier Transform Infrared Spectroscopy (FTIR)

Neat polyvinylpyrrolidone spectrum had a broad band at 3440 cm^{-1} that was due to the stretching in the amine group N-H and a medium band at 2925 cm^{-1} , which 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 the sharpest band was at 1662 cm^{-1} , and the rest of the noise bands were due to the aromatic C-H bending motion. FTIR spectrum of pure ibuprofen showed a 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} . The main functional groups in the pure ibuprofen spectrum showed an intense and well-defined absorption band at 1620 cm^{-1} due to carbonyl stretching of propanoic acid segment group, and at 3000 cm^{-1} due to hydroxyl stretching. At 1700 cm^{-1} there was a small band due to the aromatic C=C bond bending. Moreover, 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 pure ibuprofen spectrum at 1620 cm^{-1} . This indicated the breakage of the ibuprofen-ibuprofen interactions due to hydrogen bonding, which are characteristics of the

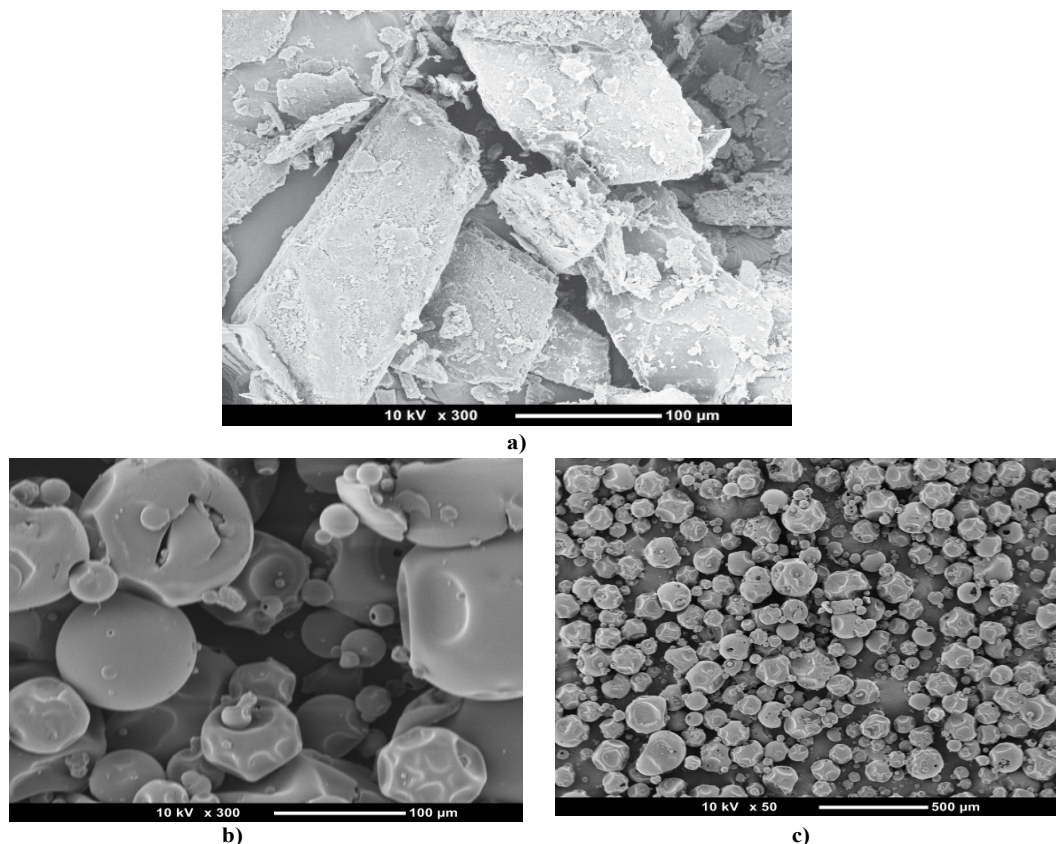


Figure 2: SEM images of ibuprofen (a), polyvinylpyrrolidone (b), microcapsules (c).

solid form of this drug. Once ibuprofen molecules were encapsulated into PVP, the carbonyl group band at 1620 disappeared.

Spectrum of microcapsules (Figure 3) show that all drug-polymer samples had the broad band due to the stretching of the N-H group, at 3440 cm^{-1} , almost similar to the pure PVP spectra. Another notable change in the spectra was a decrease in the band to a value of 1636 cm^{-1} , which was a shift 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. A small band at 1620 cm^{-1} appeared in the microcapsules spectrum, due to the stretching motion of the carboxylic acid group, similar to the ibuprofen FTIR spectrum as an indicator of the presence of the drug and the polymer in the microcapsule. Comparing this band with the drug and the polymer spectrum, it can be concluded that this band was 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 $1550\text{-}1600\text{ cm}^{-1}$ 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 hydrogen 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 $1550\text{-}1600\text{ cm}^{-1}$, corresponding to the bending motion of CO_2 , which is a strong indication of CO_2 interaction with the polymer. However this splitting in the bending motion tended to disappear once ibuprofen was encapsulated into PVP, indicating that in such a case

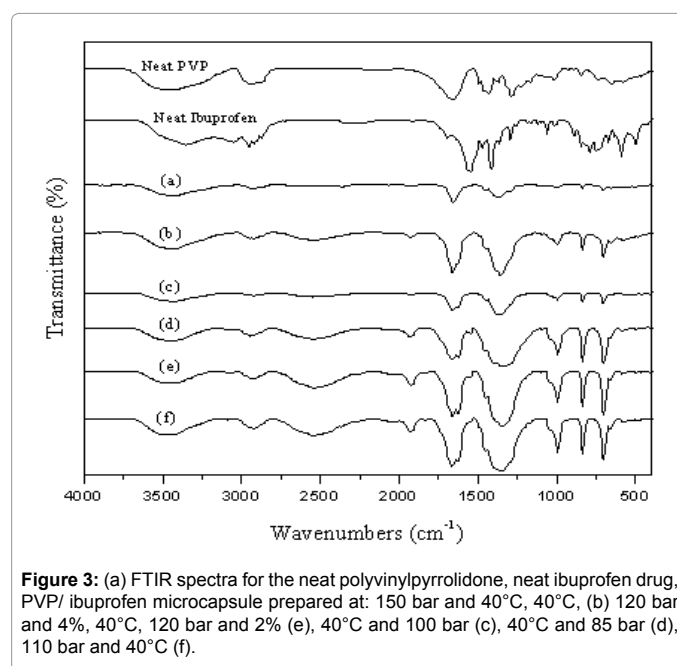


Figure 3: (a) FTIR spectra for the neat polyvinylpyrrolidone, neat ibuprofen drug, PVP/ ibuprofen microcapsule prepared at: 150 bar and 40°C , 40°C , (b) 120 bar and 4%, 40°C , 120 bar and 2% (e), 40°C and 100 bar (c), 40°C and 85 bar (d), 110 bar and 40°C (f).

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 seems to be interacting more strongly with C=O groups of PVP. Some CO_2 molecules were still

interacting with C=O groups of PVP, and this was shown by the fact that some distortion of the bending motion of CO₂ still existed after ibuprofen was encapsulated. On the other hand at the higher pressure of 150 bar, which is presented at spectrum a (Figure 3), 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.

Transmission Electron Microscopy (TEM)

TEM images of the neat polyvinylpyrrolidone showed needle shape particles with a dark color as shown in Figure 4. The size of the polymer particles was less than 1 micron, whereas the ibuprofen drug showed a darker color in contrast to the polymer. The TEM image showed particle sizes ranging between 10 microns and 100 microns of star shape particles. In the case of the polyvinylpyrrolidone/ibuprofen microparticles, which were prepared at 40°C, 120 bar, 4% drug-polymer solution to CO₂ 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. When temperature was increased by 15 degrees at 50°C, TEM images showed the ibuprofen/ polyvinylpyrrolidone microparticles of similar size to those observed in neat ibuprofen 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.

Differential Scanning Calorimetry (DSC)

The DSC results of pure PVP (Figure 5a) showed the glass transition temperature, which represents a slight shift in the slope of the baseline at 155°C of the recorded DSC thermogram. This was due to the sample undergoing a change in the heat capacity as the temperature was increased with no formal phase change. An apparent endothermic peak at 200°C, which appears soon after the glass transition temperature is attributed to the melting temperature of the crystalline phase within the polymer. At 450°C, the polymer started to decompose. DSC results of pure ibuprofen started with a broad endothermic peak caused by the loss of moisture content in the drug, which appeared at 100°C (Figure 5b). At a higher temperature, an endothermic peak appeared due to thermal decomposition of the drug. It is desirable to process the drug at temperatures below decomposition temperature to preserve the integrity of the drug. DSC results of the PVP/ibuprofen microcapsules (Figure 5c) showed that the glass transition temperature has shifted to a lower temperature due to the plasticization effect of the drug, which coincides with the endothermic peak of the drug due to moisture loss. 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 neat ibuprofen was also observed for the prepared PVP/ibuprofen microparticles using SC CO₂, 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.

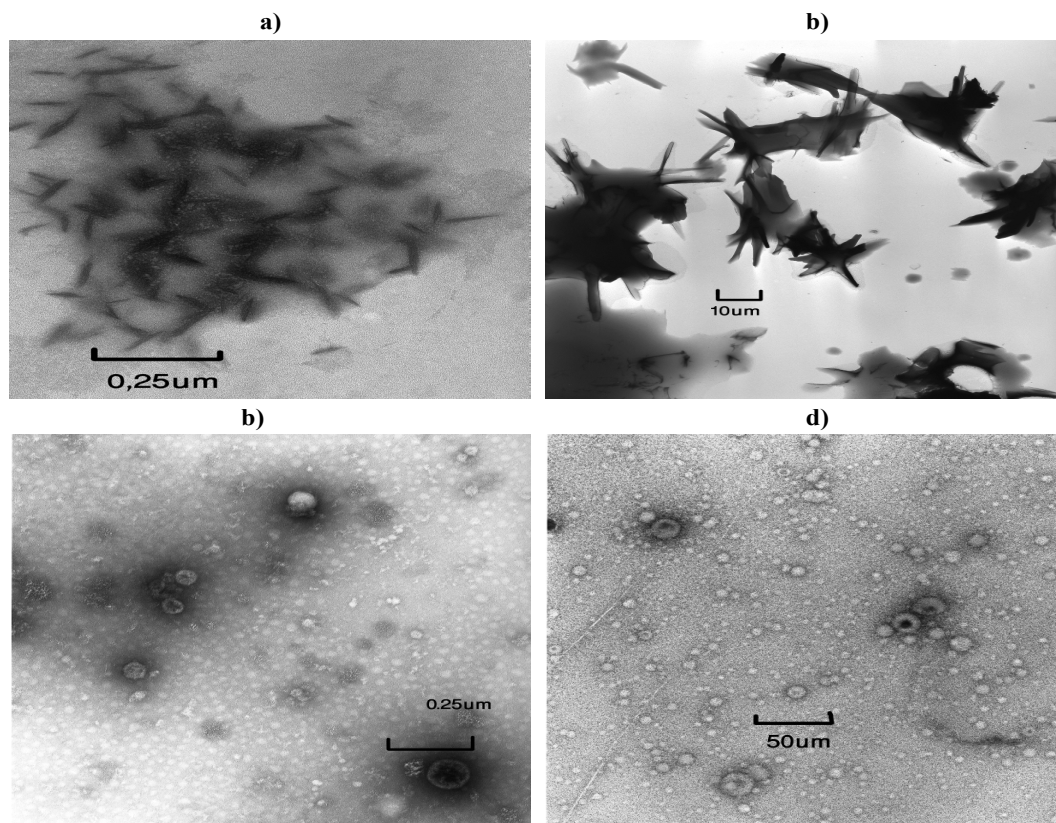


Figure 4: (a) Transmission electron micrograph of polyvinylpyrrolidone, (b) ibuprofen, (c) PVP/ ibuprofen microcapsule prepared at: 40°C, 120 bar, 4% volume ratio, (d) 50°C, 120 bar, 4% volume ratio.

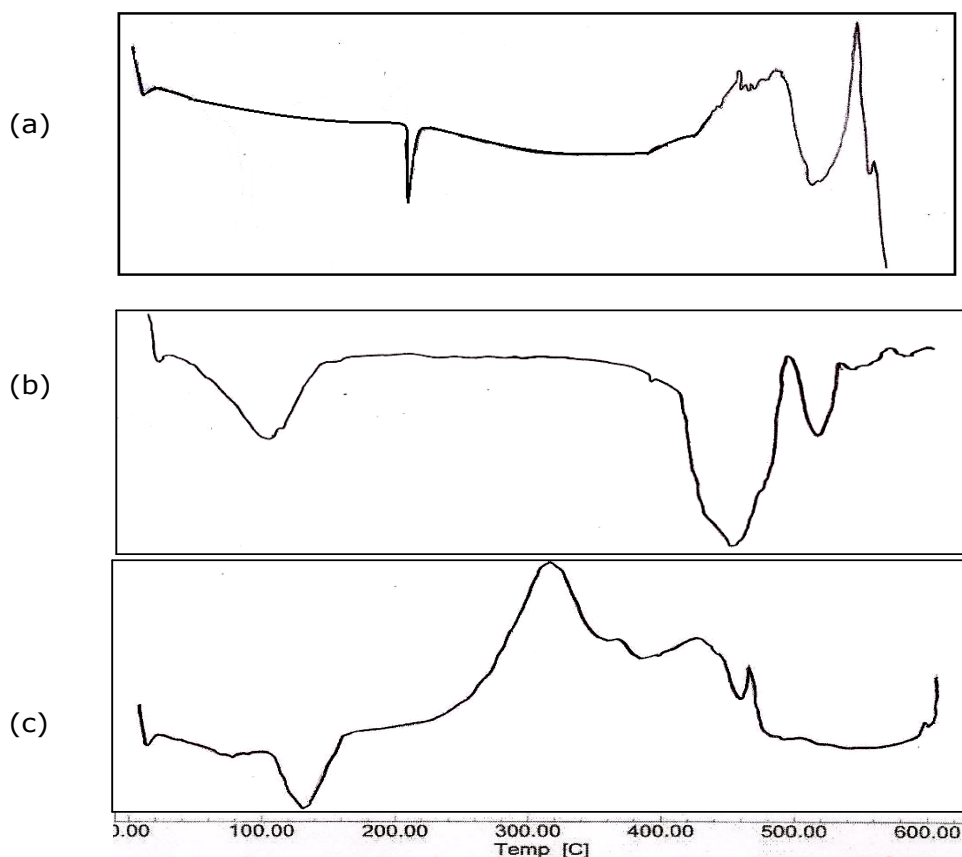


Figure 5: (a) Differential scanning calorimetry thermograms for the neat polyvinylpyrrolidone, (b) pure ibuprofen, (c) PVP/ ibuprofen microcapsule prepared at: 40°C, 150 bar, 4% volume ratio.

Thermogravimetric Analysis (TGA)

The TGA diagram obtained for the pure ibuprofen showed a very small decrease at around 100°C, due to the loss of moisture and a more significant loss at about 200°C. The polymer also lost its weight (about 12%) at around 120°C. However, the major weight loss (about 70%) in the polymer occurred at around 410°C. The TGA diagram of the microparticles showed clearly the different regions of weight loss associated with the drug and the polymer. This was clear where the capsule lost 35% of its weight at up to 300°C, which was due to drug weight loss, and 55% loss at up to 400°C due to PVP weight loss. This indicates that the microcapsules contain two different materials namely ibuprofen and PVP, and this was used to confirm the presence of two phase system in the microcapsule sample which was also confirmed by FTIR spectra, which showed different peaks of the PVP and the ibuprofen in the IR spectrum of the prepared microcapsules.

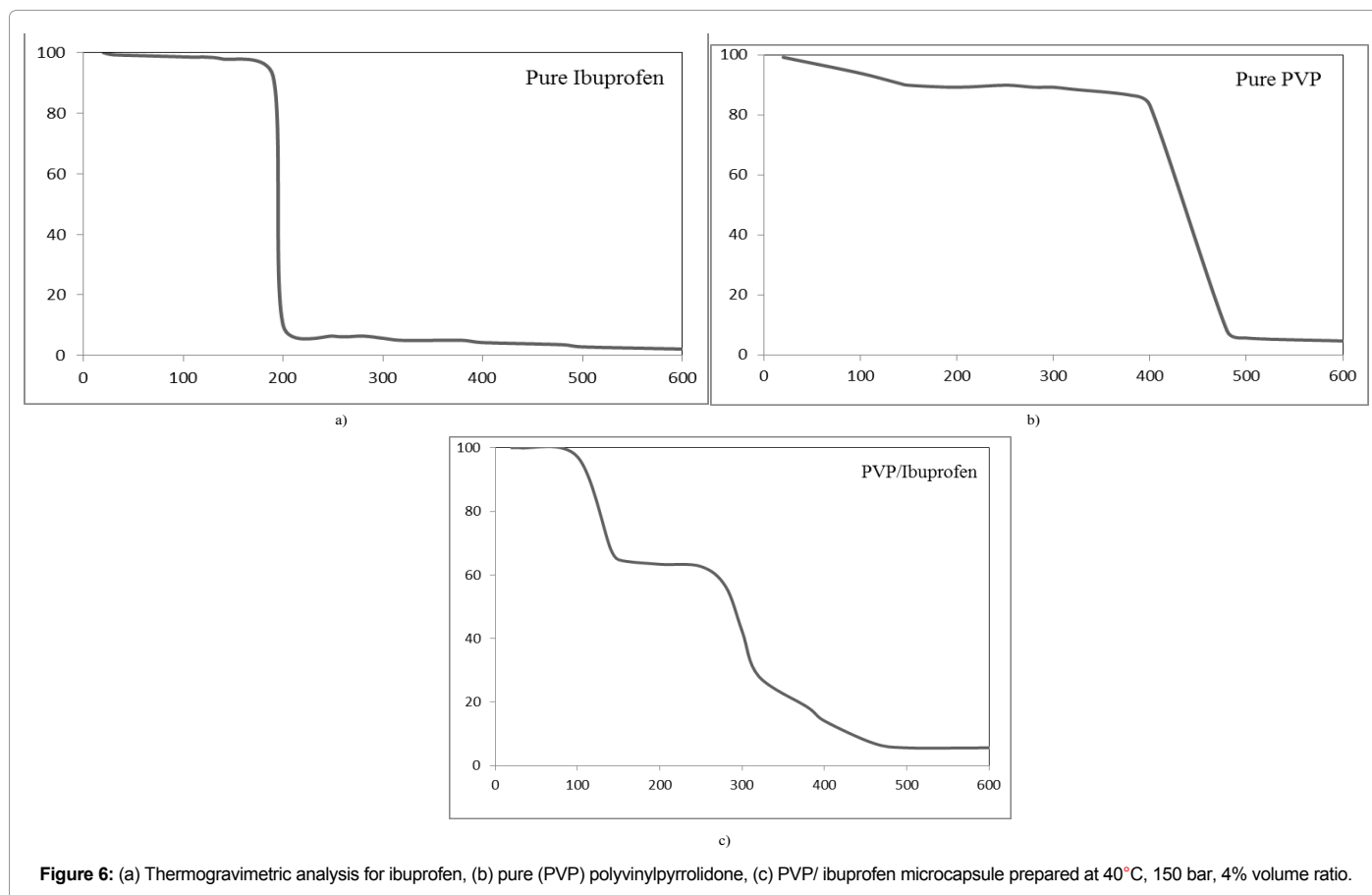
Dissolution rate study

Dissolution profiles of samples prepared at different 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 6. The highest absorbance of ibuprofen 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, 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. Ibuprofen that is inside the polymer matrices might be amorphous and easier to be released than if the drug and polymer were simple mixtures where they exist in their crystalline forms. On the other hand the neat ibuprofen had lower dissolution rate than the encapsulated ibuprofen into PVP, using supercritical CO₂ 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 temperature (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.

Conclusion

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 larger in size, showing agglomerated chunks. This might have been caused by the presence of traces of organic solvent in the sample. At the higher pressure, supercritical CO₂ could remove the organic solvent due to the higher solubility of the solvent in supercritical CO₂ at elevated pressures. Therefore, microparticles prepared at the higher pressure (e.g., 120 bar)



were well separated with uniform shape and size. This was confirmed from the doublet peaks of the FTIR test for the microcapsules, which were prepared at lower pressures (i.e., 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 CO₂ at higher flow rates prevents the supercritical CO₂ 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 microparticles. 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 comparison 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 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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