

CHALMERS



Investigating Polymer Conformation in Poly (Ethylene Oxide) (PEO) Based Systems for Pharmaceutical Applications

A Raman Spectroscopic Study of the Hydration Process
of PEO Tablet

Master of Science Thesis [in the Master Degree Programme, Advanced Engineering
Materials]

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Göteborg, Sweden, 2011

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INVESTIGATING POLYMER CONFORMATION IN POLY (ETHYLENE OXIDE) (PEO) BASED SYSTEMS FOR PHARMACEUTICAL APPLICATIONS

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ABSTRACT

The purpose of this work is to investigate the relation of hydration and the degree of crystallinity for poly (ethylene oxide) (PEO) tablets using Raman spectroscopic methods and complementary thermal analysis for pharmaceutical interests. The influence of the tableting process is also investigated by measuring the degree of crystallinity and the melting point of PEO powder and tablets. The hydration of the PEO tablets is performed in different relative (RH) humidity environments and the water uptake and the degree of crystallinity of the tablets are measured by TGA and DSC. The dry and hydrated tablets are investigated by Raman spectroscopy. The low frequency region in the Raman spectrum reflects the degree of crystallinity of PEO. The DSC results show a decrease in the degree of crystallinity by tableting and the hydration process. However, the slight decrease in the degree of crystallinity of PEO does not show significant difference in the low frequency Raman spectra, only a slight broadening of the LAM band, at 280 cm^{-1} , is observed. By measuring the PEO tablet immersed in water the hydration process can be followed in-situ with Raman spectroscopy. With changes from dry (fully crystalline) to wet state (amorphous), changes in band intensity and shape are found at 230 cm^{-1} , 280 cm^{-1} , 363 cm^{-1} , 535 cm^{-1} and 580 cm^{-1} . During hydration, the bands at 230 cm^{-1} and 363 cm^{-1} decrease in intensity and the sharp LAM band at 280 cm^{-1} is replaced by the broad D-LAM band. Among the vibrational bands observed, the band at 363 cm^{-1} is the most suitable to quantitatively follow the ingress of water into the PEO tablet and the continuous decrease of the degree of crystallinity, due to the least interference of the spectral compounds.

Keywords: Poly (ethylene oxide) (PEO), Raman spectroscopy, LAM, D-LAM, degree of crystallinity, hydration

TABLE OF CONTENTS

Abstract	
Chapter 1 Introduction	1
Chapter 2 Poly (ethylene oxide) and Its Applications in Pharmaceutical Industry.....	2
2.1 Physical properties of PEO	2
2.2 Applications in Pharmaceutical Formulation or Technology	3
Chapter 3 Raman Spectroscopy	4
3.1 Raman Spectroscopy Basics.....	4
3.2 the Raman Spectrum from Polymers	6
3.3 Raman Spectroscopy Instrumentation.....	9
Chapter 4 Experimental.....	12
4.1 Materials	12
4.2 Sample Preparation	12
4.3 Optical Microscope	15
4.4 Thermogravimetric analysis (TGA)	15
4.5 Differential scanning calorimetry (DSC).....	15
4.6 FT-Raman spectroscopy.....	15
4.7 Raman Microscopy.....	15
4.8 In-situ raman measurements of tablet Hydration.....	16
Chapter 5 Results and Discussion.....	18
5.1 Properties of powder and tablet.....	18
5.2 in-situ Hydration of a PEO tablet.....	24
Chapter 6 Concluding remarks.....	32
Chapter 7 Acknowledgments	33
Chapter 8 References.....	34

CHAPTER 1 INTRODUCTION

Poly (ethylene oxide), (PEO) is a nonionic biodegradable water-soluble polymer. Pharmaceutical grades of PEO have a wide use as hydrophilic matrix for controlled released systems [1, 2] and in hydro-gels [3-5]. The dissolution rate and/or the hydration rate are the key parameters to tailor in order to obtain a desired release profile for formulation design. The directly compressed PEO tablet is by far the most widely used dosage form, having benefits to both the producers and users [6, 7].

When a tablet is immersed in water or ingested, the penetration of water will form a concentration gradient from the surface and into the tablet core, and the polymer properties will vary along this gradient. To understand the polymer properties and the hydration profile is of fundamental importance in understanding and developing the formulation functionality.

The purpose of this work is to investigate the applicability of Raman spectroscopic methods to monitor the hydration process and study the polymer conformation of a PEO at varying water contents and relate this to materials properties (crystallinity etc.) in polydisperse high molecular weight PEO samples. Measurements have been performed on tablets of PEO of different molecular weights using Fourier-transform (FT) Raman spectroscopy and Raman microscopy and complementary thermal analysis. In particular the study focuses on the low frequency region of the Raman spectrum where the longitudinal acoustic mode (LAM) and disordered longitudinal acoustic mode (D-LAM) carry information on the crystallinity and conformational changes. The crystal structure and the LAM vibration of monodisperse low molecular weight PEO have been extensively studied by low frequency Raman spectroscopy in combination with small-angle X-ray scattering (SAXS) and differential scanning calorimeter (DSC) [8,9]. However the LAM and D-LAM vibration mode of polydisperse high molecular weight PEO have not been fully investigated particularly by Raman spectroscopic methods.

This report is divided into six parts: Chapter 2 reports the basic physical properties of poly (ethylene) oxide and its applications for pharmaceuticals; in Chapter 3 the basics of Raman spectroscopy, and its application to polymers, in particular PEO, are presented; Chapter 4 and 5 are devoted to the experimental work and the results and discussion. Finally Chapter 6 summarizes the conclusions of this work.

CHAPTER 2 POLY (ETHYLENE OXIDE) AND ITS APPLICATIONS IN PHARMACEUTICAL INDUSTRY

2.1 PHYSICAL PROPERTIES OF PEO

The chemical structure of the repeating unit of PEO is shown in Figure 2-1. The polymer chain has two terminal groups, -H and -OH. The repeating unit contains a hydrophobic ethylene unit and hydrophilic oxygen, which is also a hydrogen bond site. Poly (ethylene oxide) (PEO) is prepared by polymerization of ethylene oxide (EO) using a suitable catalyst. Low molecular weight PEOs (MW<20,000) are also referred to PEGs and they are colorless liquids or waxy solids depending on their molecular weights. High molecular weight PEOs (MW>20,000) are highly crystalline thermoplastic solids.

X-ray analysis [10] have shown that the crystal structure of PEO has a helical conformation containing seven structural units $-(O-CH_2-CH_2)-$ with two helical turns per fiber identity period 19.3\AA , a 7_2 helix, which is constructed with a succession of trans (CCOC), gauche (OCCO) and trans (COCC) bonds along the chain, see Figure 2-2.

PEOs are commercially available in a very wide range of molecular weights from 200 to 7×10^6 g/mol. There are often narrow polydispersity products available. PEOs have good mechanical properties even though they have a low glass transition temperature, $T_g = -52^\circ\text{C}$. They are completely soluble in cold and warm water. The similarity of the ether oxygen spacing (2.88\AA) with that of the oxygen in water (2.85\AA) has been suggested to explain the good solubility [11]. The pH of PEO solutions is in the range from 6.5-7.5 [6].

POLYOX Water-soluble resins (WSR), produced by the Dow Chemical Company, are commonly used PEO for pharmaceutical and hygiene products. There are several grades of POLYOX available for different uses. All grades are white to off-white powders or granulates. They have a bulk density of $\sim 500\text{ kg/m}^3$. For pharmaceutical applications, fumed silica (silicon dioxide) (up to 3% by wt) is added as an antioxidant and also to improve powder flow properties in high speed compression production [2].

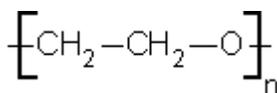


Figure 2-1 Repeating unit of PEO. n represents the polymerization degree, which is the number of repeating units.

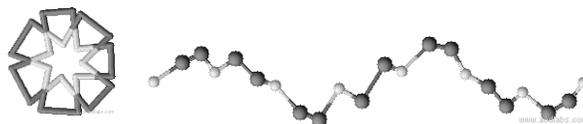


Figure 2-2 Schematic structure of the 7_2 helical conformation structure of the polymer chain in the PEO crystal (redrawn from ref [10]).

2.2 APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Poly (ethylene oxide) is a biocompatible polymer and it found in diverse applications in pharmaceutical industry, such as matrix for controlled release system, tablet binder for direct compression, mucosal bioadhesive, thickening agent, and tablet coating [2]. PEOs are nonionic, nontoxic, nonirritant, and generate no residues, sediment or vaporous elements and their applications in drug delivery systems are extending. As a good candidate material for novel hydrophilic matrix system, PEO has gained great attention from scientists and industry. It could potentially be used to achieve constant-rate delivery of high soluble bioactive agents over an extended period because of its pH-independent zero-order kinetics as a hydrophilic swellable polymeric matrix [12]. Furthermore both immediate-release [3] and extended-release [4] can be achieved by blending PEO with different molecular weights or with various other polymers and other excipients.

The release behavior of a hydrophilic swellable matrix involves diffusion and erosion. Based on these release mechanisms, it is important to understand the dissolution behavior of the polymeric matrix associated with its material properties, such as crystallinity, mobility, and melting point. Yet the dissolution mechanism of semicrystalline polymers is still not well understood. For drug release systems based on a semicrystalline polymer, a crystal dissolution-controlled release system has been proposed where the drug release is controlled by the rate of crystal dissolution in water [13]. The crystal dissolution-controlled release systems based on poly (vinyl alcohol) (PVA) and PEG have been investigated regarding the degree of crystallinity and the lamellar thickness of the crystals [13, 14]. Mallapragada [15] proposed a dissolution mechanism of semicrystalline poly(vinyl alcohol) (PVA), where in the presence of a solvent the chains of the crystal unfold layer by layer and join the amorphous phase surrounding them. The amorphous phase subsequently dissolves.

In this work we use Raman spectroscopic methods to monitor the dissolution process of semicrystalline PEO by measuring the conformational changes and associate this to the degree of crystallinity measured by differential scanning calorimeter (DSC).

The crystallinity can also be influenced by the manufacturing process through eg. shearing or during tableting [15]. Assuming the crystallinity probably is a result of the structural irregularities in the crystal lattice caused by shearing, stressing, and slip planes. Because of the viscoelastic behavior and large axial deformation of PEO during tableting, the tensile strength of tablets is relatively low. Hence the variance of the degree of crystallinity changes caused by pressing is also of interest in this work and has been measured by DSC and Raman spectroscopy.

CHAPTER 3 RAMAN SPECTROSCOPY

3.1 RAMAN SPECTROSCOPY BASICS

Raman spectroscopy is a powerful tool for the analysis of materials and chemicals. It can be used for both quantitative and qualitative analysis and can also be deployed in-line in production. Raman spectra can provide information on chemical structure and composition and be used to monitor polymerization processes and polymer degradation mechanisms. It can also be used to determine crystallite dimension and orientation. In this work Raman spectroscopy has been used to measure the conformational order of the PEO chains during the hydration process and tablet pressing associated with the changes of the degree of crystallinity.

Raman scattering is inelastic scattering of a light (photons) and was first reported by Dr. C. V. Raman in 1928 [17]. The principle of this phenomenon is described in Figure 3-1. The scattered light, which has the same frequency as the incident light, ν_0 , is called Rayleigh scattering. There is a very small portion [18] of the scattered radiation which does not have the frequency ν_0 , inelastic scattering, which is called Raman scattering. The scattered light may lose or gain energy, and therefore decrease or increase in frequency. The former is called Stokes Raman scattering and the latter is called anti-Stokes Raman scattering. The amount of Stokes scattering is much greater than anti-Stokes scattering so normally only the Stokes scattering is measured. The energy difference $\Delta E = h(\nu_0 - \nu_i)$ corresponds to the energies of the light inelastically scattered by the sample, where ν_0 is the frequency of the incident light and ν_i the frequency of a molecular vibration.

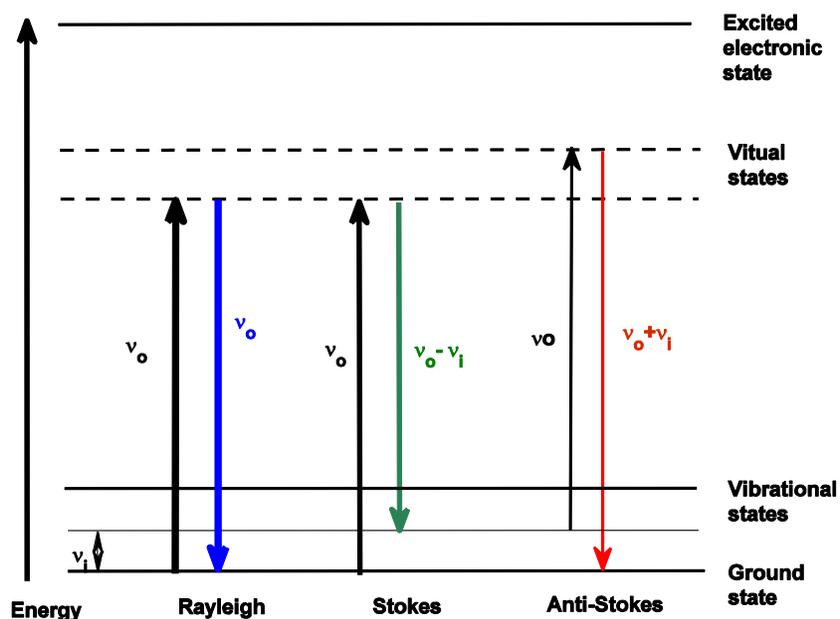


Figure 3-1 Diagram of energy transitions of Rayleigh and Raman scattering.

Raman scattering arises from the interaction between the light and the material due to a change in polarizability as a molecular vibrates. The polarizability α is defined as the ratio of the induced dipole moment μ of an atom to the electric field ϵ that introduces this dipole moment.

$$\alpha = \frac{\mu}{\epsilon} \quad (3-1)$$

Polarizability is a molecular property that varies depending on atomic species, molecular structure and the surrounding environment of the molecule. Therefore the frequency and the shape of the Raman bands related to the molecular vibrational modes are determined by the properties of the investigated material on a molecular.

Raman spectroscopy can provide information about the symmetry of a vibration. This can be investigated by measuring the polarized (I_{VV}) and depolarized (I_{VH}) Raman spectra. The polarization analysis and the different polarization character of the spectral contributions are shown through the evaluation of the isotropic contribution:

$$I_{iso} = I_{VV} - \frac{4}{3}I_{VH} \quad (3-2)$$

The spectrometer polarization efficiency can be evaluated by the depolarization ratio, ρ , which is given as:

$$\rho = \frac{\Phi_{\perp}}{\Phi_{\parallel}} \quad (3-3)$$

where Φ_{\parallel} and Φ_{\perp} are the intensities of the Raman scattered light with polarization parallel and perpendicular to the polarization of the incident light, respectively. Carbon tetrachloride (CCl_4) is commonly used to obtain this parameter. Carbon tetrachloride has a well-defined highly polarized ($\rho=0.005$) Raman band at 459 cm^{-1} , which is related to the symmetric stretching mode [19]. The measured depolarization ratio of the JY Horiba LabRAM spectrometer is reported in Section 4-7.

3.2 THE RAMAN SPECTRUM FROM POLYMERS

A Raman spectrum from a polymer can be approximately divided into five regions:

- The X-H stretching region (2500-4000 cm^{-1}): the vibrations in this region are due to O-H, N-H, and C-H stretching. O-H stretching produces a broad band in the range 3100-3650 cm^{-1} which is normally weak in FT-Raman experiment because of the very low efficiency of the detector in this region.
- The triple (2000-2500 cm^{-1}) and double bond region (1500-2000 cm^{-1}): Triple and double carbon bonds can be found in many polymers. Typically the polymerization process and degradation mechanism can be monitored and analyzed by investigating this region using Raman techniques.
- The skeletal vibrations/fingerprint region (400-1500 cm^{-1}): the spectrum of this region is typical of a molecule. The reason that this region is referred to as fingerprint region is that each band can be assigned to a particular deformation of a polymer, the movement of a group of atoms, or the bending and stretching of a particular bond. However there are also often interactions between different molecular vibrations giving mixed vibrational modes.
- Far-infrared region (below 400 cm^{-1}): this region provides information regarding crystal lattice vibrations which are associated with the movement of the chains with respect to each other in crystalline solids. The bands of interest in this work (LAM and D-LAM band) occur in this region and will be introduced in Section 3.2.

Figure 3-2 shows a Raman spectrum of a PEO powder ($M_w=600\ 000$, Sigma-Aldrich) measured with a Fourier-transform (FT) Raman spectrometer (Bruker ISF66 with a 1064 cm^{-1} laser and 2 cm^{-1} resolution). As shown in Figure 3-2, PEO has strong C-H stretching bands between 2800 and 3000 cm^{-1} and no bands in the double or triple region are observed according to its molecular structure. Raman studies in the fingerprint region can be used to investigate the polymer conformation of PEO in different states and different solutions [21]. For instance, the band at 862 cm^{-1} in the crystalline state, related to the ordered helical conformation, is a complex mode involving an ethylene rocking mode and a backbone stretching vibration. This band also shows a frequency dependence depending on the water concentration in PEO solutions [21].

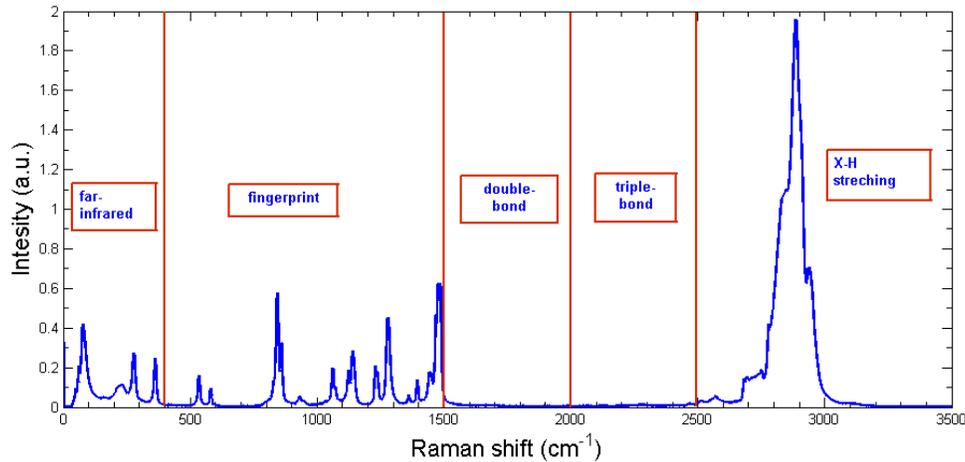


Figure 3–2 FT-Raman spectrum of dry PEO sample. ($M_w=600,000$)

3.2.1 LONGITUDINAL ACOUSTIC MODE (LAM)

The strongly polarized longitudinal acoustic mode (LAM) of polymers has been used as a morphological tool to study polymer crystallization through the skeletal vibrations of the crystalline stem within a lamella [9]. The LAM mode for all-trans n-alkanes chain is a symmetric accordion-like longitudinal vibration and appears at very low frequencies, around 20 cm^{-1} to 200 cm^{-1} [23]. The frequency of the mode has been found to be inversely proportional to the length of the chain undergoing this vibration [8]. For polyethylene and n-alkanes, the frequency of the LAM, $\nu_{LAM} (\text{cm}^{-1})$ is described by [23]:

$$\nu_{LAM} = \frac{1}{2cL} \left(\frac{E}{\rho} \right)^{\frac{1}{2}} \quad (3-4)$$

where E is the Young's modulus of the chain, ρ is the single chain density, L is the length of vibrating chain segment, and c is the speed of light. It has been shown that the longitudinal interactions between crystal lamellar may modify this relation [8]. For helix polymers such as PEO, significant lateral interactions within a polymer chain shift the LAM frequency [8]. The frequency can also be changed by altering crystallization parameters (crystallization temperature, T_c , crystallization time, t_c , and pressure etc.) [8] resulting in changes in the crystalline arrangement. The LAM mode has a characteristically high intensity due to the large change in polarizability associated with the long-chain motion.

3.2.2 DISORDERED-LONGITUDINAL ACOUSTIC MODE (D-LAM)

In non-crystalline systems the presence of conformational disorder dramatically changes the low-frequency Raman spectrum. The narrow LAM band is replaced by the much broader D-LAM band where D stands for disordered. It is a unique Raman band in the low-frequency region and can provide information on long-range conformational disorder in polymers with highly disordered chains [22].

The D-LAM band is distinguished from almost all other bands in isotropic spectra. A good spectrometer efficiency is crucial for D-LAM band measurements. In previous studies, both isotropic and polarized Raman spectra were used to analyze the D-LAM band [20]. In this work, only polarized Raman spectra are reported due to limited spectrometer efficiency.

The D-LAM band has been identified in isotropic Raman spectra of many polymers such as polyethylene, poly (tetrafluoroethylene), poly (ethylene oxide) and polybutadiene [22]. The position and shape (half bandwidth) of the D-LAM band are directly related to the conformational statistics [22]. The band itself has a low depolarization ratio so that it can be distinguished from almost all other kinds of bands in the low-frequency Raman spectrum.

As we have been discussed above, the D-LAM band depends on the statistical distribution of all-trans chain segment. In contrast to the $1/n$ dependence observed for the LAM modes of ordered chains, where n is the polymerization degree, a different experimental relation is found from the D-LAM mode [24]:

$$\nu_{D-LAM} = \nu_0 + B/n^2 \quad (3-5)$$

For the n -alkanes the values of ν_0 and B have been experimentally determined to be 200 ± 2 and $(5.43 \pm 0.54) \times 10^3 \text{ cm}^{-1}$ [24]. Therefore this intense band appears between 200 cm^{-1} and 300 cm^{-1} .

The frequency of the D-LAM will shift to lower value as the chain length increases. Theoretically, the frequency of the D-LAM band will reach a plateau when the polymer chain length goes to infinity as shown in Equation 3-5. The oligomer ethylene oxide (EO) has a ν_{D-LAM} at around 350 cm^{-1} [20]. Increasing the molecular weight, the D-LAM frequency shifts towards to lower value as predicted from Equation 3-4 and 3-5. However, when the molecular weight is greater than 600, a plateau is reached. Taken together with the analysis from Brillouin spectroscopy, PEO has an oligomer to polymer transition for M_w around 600 [20]. This value defines the minimum length for when a polymer is polymeric in behavior [25], such as the in viscoelastic response.

3.2.3 D-LAM FREQUENCY OF PEO/WATER SYSTEM

For PEO of $MW=600$ (liquid state), the ν_{D-LAM} is found at 264 cm^{-1} ; for PEO 600 ($M_w=600$) in 25% aqueous solution, ν_{D-LAM} is at 286 cm^{-1} which is close to that LAM frequency in crystalline state, around 284 cm^{-1} [22]. This indicates that the presence of water gives a more ordered conformation in solution. The reason is that the concentration of gauche conformation of C-C bonds is increased in the diluted solution. This conformation is favored due to hydrogen bonds between water molecules and the ether oxygen in the polymer chains. Thus, in PEO water solution, the polymer chain is bonded by water molecules and a more rigid hydrated coil is formed.

The presence of water also destroys the crystal structure. At a certain amount of water full hydration of the polymer will be reached and all the crystalline parts are melted. Trotzic [26] has reported that the degree of crystallinity is found to be only 0.004 at water fraction of 0.5% w/w for PEO of $MW 100,000$. Apicella et al. [27] examined the penetration, swelling and dissolution behavior of PEO 600,000 and showed that the water penetration along

depth is almost linear as a function of time and a rapid water penetration rate in a very short initial transient.

In this thesis the main purpose is to follow the PEO dissolution process from the very beginning to its full hydration by investigating the crystalline and amorphous distribution using Raman spectroscopic methods.

The temperature dependency of the D-LAM band of PEO have been evaluated by Raman scattering [20]. The frequency and bandwidth of D-LAM have different behaviors with increasing temperature. In this work, the temperature in all experiments was $23 \pm 1^\circ\text{C}$. Since the variance of temperature is very small, the frequency shifting and band broadening due to temperature effects of the D-LAM band are negligible.

3.3 RAMAN SPECTROSCOPY INSTRUMENTATION

The advantages of Raman spectroscopy can be described as following: (1) water is an ideal solvent because its Raman spectrum is weak and it does not absorb the laser irradiation and it is not heated by the light. For biological research, water is a perfect medium; (2) much better sensitivity to carbon-carbon bonds compared to infrared absorption; (3) there is almost no sample preparation required and fewer restrictions concerning sample size and form: solids, liquids, polymers, tablets, papers and living cells can all be investigated. Opaque or colored samples can also be tested. Measurements can be carried out through many containers such as glass bottles or plastic containers. Raman scattering is also considered as a non-destructive technique since it does not cause any sample damage especially when using long wavelength laser; (4) implementation of 2D detectors (Charge coupled device or CCD cameras) allows one to multiplex several sampling points with separate optical fibers delivering signals from each [28].

One of the principle problems in Raman spectroscopy is fluorescence. For many samples a Raman spectrum cannot be obtained because it is hidden by fluorescence in the visible region. Fluorescence occurs when the excitation line is partially absorbed and reemitted. To overcome this problem, several techniques have been successfully developed including Fourier transform Raman spectroscopy and near infrared Raman spectroscopy. "Bleaching" the sample can also help to minimize fluorescence.

3.3.1 FT-RAMAN SPECTROSCOPY

The main components of the FT-Raman instrument include: (1) a near IR laser as excitation source, commonly a Nd: YAG laser at 1064 nm (9398 cm^{-1}), (2) a interferometer, (3) a detector for the near-IR region, usually an InGaAs detector, (4) a sample chamber with optical elements matching the FT-instrument, and (5) an optical filter that cuts off the Rayleigh-scattered light. A diagram of such a FT-Raman instrument is shown in Figure 3-3. Fourier transform Raman spectroscopy is designed to eliminate the fluorescence problem encountered in conventional Raman spectroscopy due to the employment of long wavelength laser.

Unlike grating spectrometers, the entrance aperture of an interferometer is not a narrow slit, but a larger, circular aperture called the Jacquinot stop. This aperture is necessary to

limit the beam to those rays which can interfere, depending on the spectral resolution [29]. If the incident beam completely fills the aperture and the beamsplitter, the signal that reaches that the detector can be maximized. Thus relatively large samples are examined which explains the great success of FT-Raman spectroscopy for bulk materials with respect to dispersive techniques. However the major disadvantage of FT-Raman spectroscopy is a considerable loss in sensitivity because of the long wavelength of the incident beam.

In this work, FT-Raman spectroscopy is used to measure neat PEO in form of dry powder and compressed as tablet in order to get good quality spectra with less or no background to use as control spectra compared to those from the treated samples.

3.3.2 RAMAN MICROSCOPY / NIR RAMAN MICROSCOPY

Raman microscopy is a suitable analytical tool for examining different types of materials from minerals and polymers, cells and proteins. A Raman microscope instrument is generally comprised of a standard optical microscope, a laser in visible region, a grating system, and a detector (such as a charge-coupled device (CCD)). A diagram of Raman microscope is shown in Figure 3-4.

In this work, a JY Horiba LabRAM has been used. It has a 785 nm excitation diode laser, which is used to overcome the fluorescence problem and a microscope system to be able to get a good spatial resolution, down to 1 μ m. The NIR excitation also reduces the risk of sample burning or destruction of biological and biomedical samples. However, the limitation of a 785 nm diode laser is a lower in intensity of Raman scattering and hence an increased integration time compared to shorter wavelength lasers.

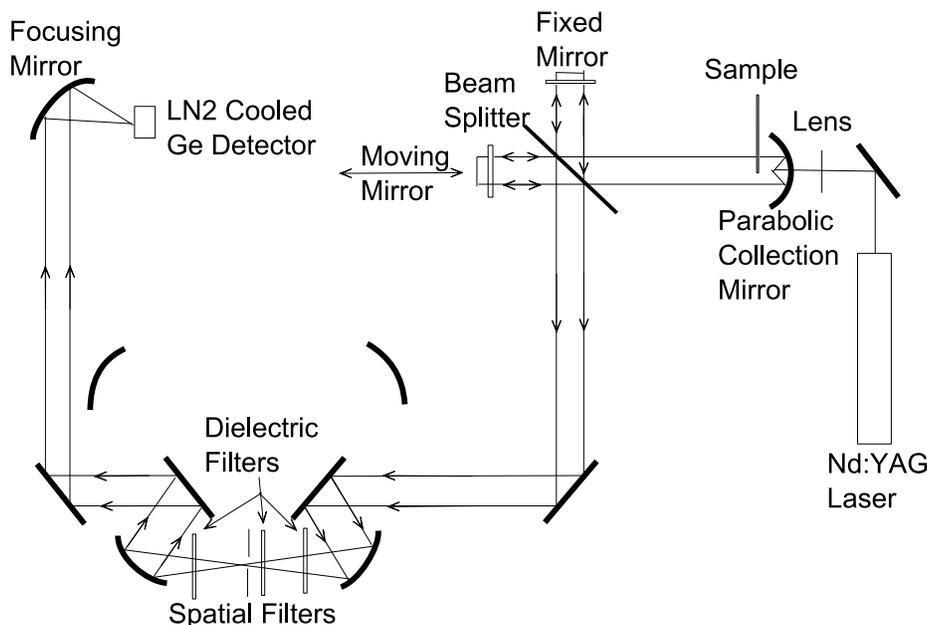


Figure 3-3 Optical diagram of an Fourier transform Raman spectrometer. (Redrawn from ref [29])

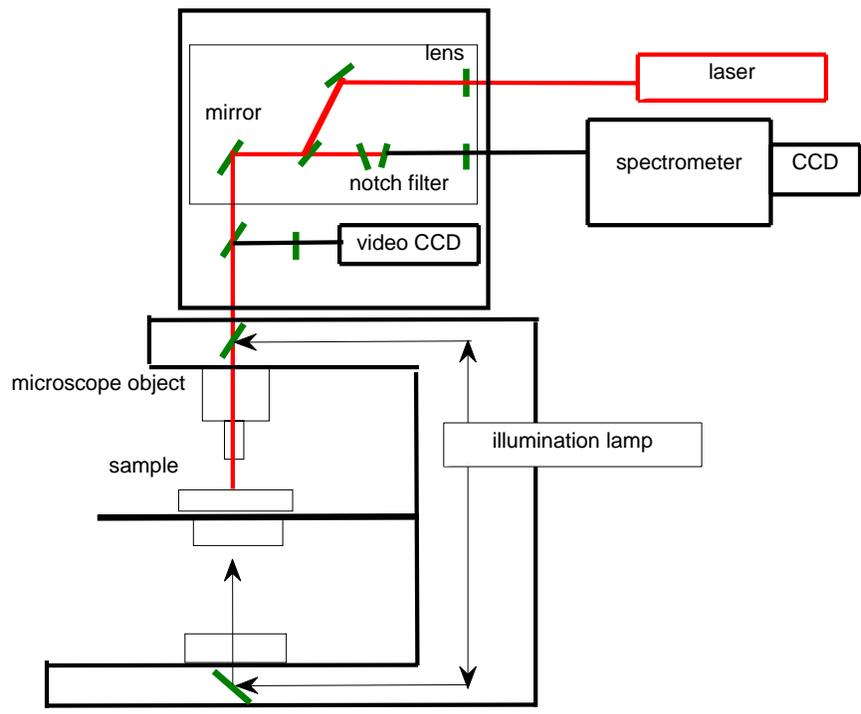


Figure 3-4 Schematic diagram of a Raman microscopy instrument.

CHAPTER 4 EXPERIMENTAL

In this chapter the materials used, sample preparation and evaluation methods are described.

4.1 MATERIALS

Four PEOs with different molecular weights have been studied. Polyox™ WSR N-10 (hereafter referred to as PEO0.1) and Polyox™ WSR N-60K (hereafter referred to as PEO2.0) are produced by Dow Chemical Company especially for pharmaceutical applications. The other two PEOs are from Sigma-Aldrich® and Polysciences, Inc. (hereafter referred to as PEO 0.6 and PEO 4.0, respectively). The molecular weights and some specifications of each material are given in Table 4-1.

4.2 SAMPLE PREPARATION

The sample preparation can be divided into two parts. One is to produce the PEO tablet by direct compression and followed by the hydration process. The final sample is obtained when the hydration process reached equilibrium. Thereafter, a well-prepared hydrated tablets are ready to be measured.

4.2.1 TABLETING

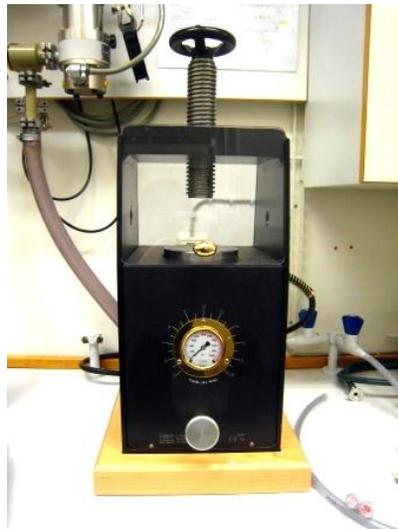
Tableting was performed on a laboratory press with 13 mm die set (Air-EZ™ Air-powdered 20 Ton Automated Lab Press and 13 mm die set, International Crystal Laboratories). The maximum compression force was 4000 psi (equal to 27 MPa). The target tablet was flat-faced. The weight was 300 ± 10 mg and the thickness was 2 mm. The Air-EZ™ lab press equipment and a produced tablet are showed in Figure 4-1.

4.2.2 HYDRATION

Hydration of tablets was performed in different controlled relative humidity (RH) in desiccators. Saturated salt solutions were prepared to generate constant relative humidity. The procedures of preparing saturated salt solutions followed the ASTM E104 standard [36] except that tap water was used instead of distilled water. The influences of tap water on the obtained relative humidity and the PEO hydration is negligible since the aim of using saturated salt solutions was to provide controlled environment rather than obtain accurate relative humidity. Four salts were used to prepare saturated salt solutions. Lithium chloride and potassium chloride were purchased from Merck and potassium carbonate and sodium bromide from Sigma-Aldrich. Selected salts and the corresponding relative humidity are given in Table 4-2. Also distilled water was used to obtain 100% relative humidity environment.

Table 4–1 Specifications of PEO samples. All information is from the official websites of each company. The values not supplied by the manufacturer are indicated as “—”

	PEO 0.1	PEO 2.0	PEO 0.6	PEO 4.0
Source	Dow Chemical	Dow Chemical	Sigma-Aldrich	Polysciences, Inc.
Grade/Brand	Polyox™ N-10	Polyox™ N-60K	ALDRICH	Polysciences
Lot #	TG1355S5HI	PL0555S520	14106HI	64299
Mol. Wt.	100,000	2,000,000	600,000	4,000,000
Fumed silica (Silicon dioxide)	≤3.0%	≤3.0%	—	—
Alkalies and Other Metals % by wt as CaO,	≤2.0 %	≤2.0 %	≤2.0 %	—
BHT as inhibitor/antioxidant	100-500 ppm	100-500 ppm	200-500 ppm	—



(a)



(b)



(c)



(d)

Figure 4-1 (a) the press, and (b) the die set, and (c-d) the resulting compressed tablet.

Table 4-2 Equilibrium relative humidity (RH) obtained with the saturated salt solutions. Values are adapted from literature [36] and are not measured in this work.

Salt	Formula	RH % (20°C)	RH % (25°C)
Lithium chloride	LiCl	11.3±0.31	11.3±0.27
Potassium carbonate	K ₂ CO ₃	43.2±0.30	43.2±0.40
Sodium Bromide	NaBr	59.1±0.40	57.6±0.40
Potassium chloride	KCl	85.1±0.29	84.3±0.26

Once the saturated salt solutions were ready, each of them was put into a small desiccator and equilibrated for 24 hours before hydration of the tablets. The desiccators stored in a room with the temperature set at $23\pm 1^\circ\text{C}$. Three tablets were made for each PEO in each relative humidity.

4.3 OPTICAL MICROSCOPE

Samples of PEO powders and tablets were examined using a Zeiss Microscope with a magnification of 5x and 20x in dark field. Obtained images provided a better understanding of the morphologies of the material on the μm length scale.

4.4 THERMOGRAVIMETRIC ANALYSIS (TGA)

The water content of hydrated PEO tablets were measured by thermogravimetric analysis (TGA) using a NETZSCH TG 209 F1 Iris® instrument. The sample was heated from 30 to 150°C , at a rate of $10^\circ\text{C}/\text{min}$, where a constant residual weight was reached. The water content was determined by the weight loss in temperature range of $30\text{-}150^\circ\text{C}$, which included the free water and a small amount of bound water.

4.5 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The thermal properties were examined by a TA Instruments DSC Q1000. 2-5 mg of sample was sealed in a hermetic aluminum pan and equilibrated at 25°C . The melting point and the degree of crystallinity were determined by heating the sample to 120°C at a heating rate of $10^\circ\text{C}/\text{min}$. The melting point was taken as the onset temperature, T_o , and the peak temperature, T_m of the melting peak.

4.6 FT-RAMAN SPECTROSCOPY

Spectra of fresh PEO powders and untreated PEO tablets were obtained with a Fourier-transform (FT) Raman spectrometer Bruker IFS 66 using a 1064 nm Nd:YAG laser and a resolution of 2 cm^{-1} . The powders were in glass vials, and the tablets were fixed to the sample holder. The acquisition times were 120 min and 20 min for powders and tablets respectively.

4.7 RAMAN MICROSCOPY

Raman measurements were performed on a JY Horiba LabRAM using a 785 nm diode laser. The resolution was 1 cm^{-1} . The acquisition time varied depending on the sample conditions. For dry tablets the acquisition time was 60 seconds for a laser power of 50-60 mW on the sample. For hydrated tablets and polymer gels the integration time was 300 seconds. In the latter case the integration time was a compromise between obtaining good spectra and tablet drying. Spectra were recorded in polarized and depolarized mode.

The depolarization ratio was determined by measuring the intensity of the 459 cm^{-1} band of carbon tetrachloride (CCl_4). This band is a highly polarized band ($\rho=0.005$), which is related to the symmetric stretching mode [31]. The recorded polarized and depolarized spectra are shown in Figure 4–2, whose intensities were normalized to the incident laser power. The calculated depolarization ratio ρ for the Raman line at 460.0 cm^{-1} is 0.053. The large value may be due to misalignment of the optical elements and/or the quality of the analyzer. However, the changes in the PEO low-frequency spectra are large so that even with this level of the depolarization ratio, the isotropic bands will still show the major trends of D-LAM band, but the quantification of the band parameters, such as the band width, will be less accurate.

4.8 IN-SITU RAMAN MEASUREMENTS OF TABLET HYDRATION

The PEO tablet was half immersed in distilled water in a Petri dish, see Figure 4–3. A Raman spectrum was measured every 3 minutes in the first 35 minutes of hydration and every 5 minutes for the next 50 minutes. A 785 nm diode laser was used and the resolution was 1.4 cm^{-1} . The measured area was close to the edge where the water penetration will start. The focus of the laser was adjusted to get the maximum intensity. The integration time was between 120s and 300s. A sketch of the sample set-up is shown in Figure 4–3.

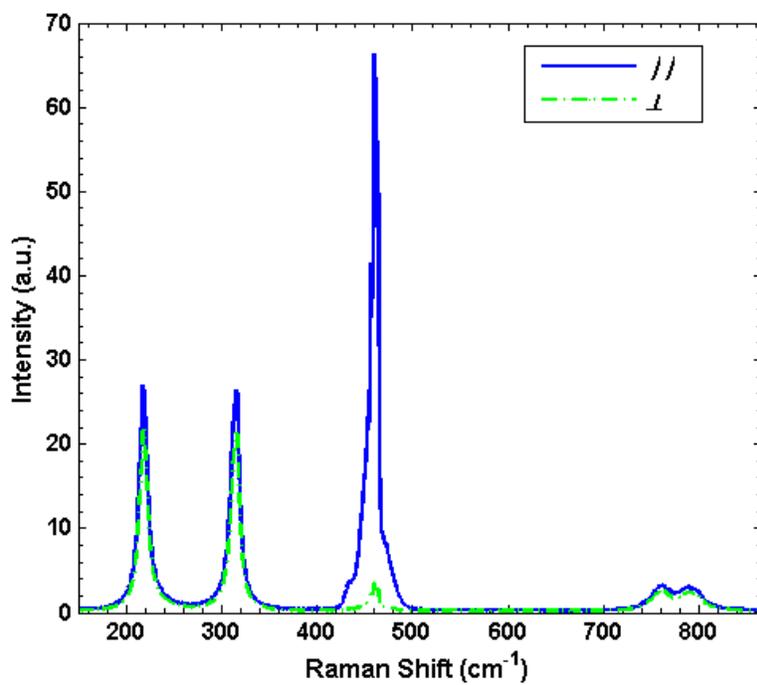


Figure 4–2 Polarized (dash-dot line) and depolarized (solid line) of Raman spectra of from CCl₄

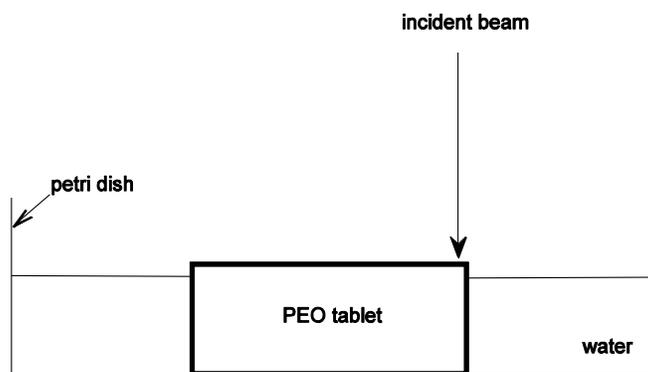


Figure 4–3 Schematic set-up of in-situ monitoring of the hydration process

CHAPTER 5 RESULTS AND DISCUSSION

5.1 PROPERTIES OF POWDER AND TABLET

The comparison of the PEO powder and the PEO tablet is discussed in this section. The morphology of PEO in form of powder and tablet, was examined by optical microscopy. Crystallinity and melting point were determined by DSC. Raman spectra were obtained by FT-Raman and LabRAM in the range of 100-500 cm^{-1} . The Raman spectrum and the DSC result of highly crystallized PEO powder (MW = 100,000) are also reported for comparison.

5.1.1 OPTICAL MICROSCOPY

An optical microscopy image of the PEO powder and the compressed tablet are shown in Figure 5-1. The particles are spherical-shaped and smooth-edged but various in size. Sieving analysis showed 96% by wt of the particles have a diameter less than 0.841 mm (20 meshes), according to the manufacturer. Studies have reported that the effect of particle size distribution on drug release profiles of resulting tablets was negligible [32]. Thus in this project non-sieved powder has been used to prepare tablets.

The surface of the tablet appears rough which may be due to the elastic recovery and relaxation after tableting. No concrete conclusion can be drawn for elastic recovery with different molecular mass [33]. The ductility during tableting can also cause the formation of a thin film around the edge. This may be induced by the high-speed shear forces causing melting of PEO particles and the formation of the film between the turret area and die wall since PEO has a low melting point, T_m around 65°C, see Table 5-1.

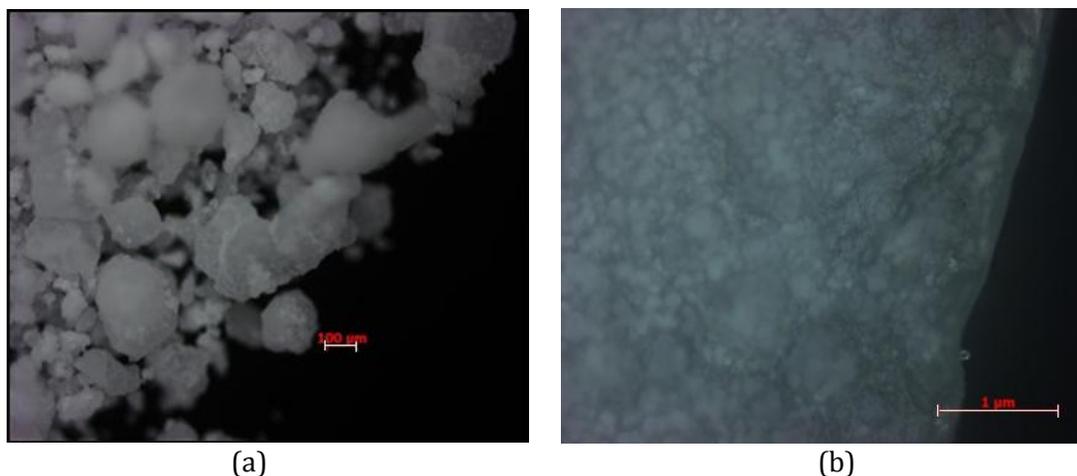


Figure 5-1 Dark field images of (a) PEO powder at 5x magnification and (b) PEO tablet at 20x magnification. Scale bars are 100 μm and 1 μm respectively. (MW=2,000,000).

5.1.2 THERMAL ANALYSIS

The DSC results of all the four PEO samples show a similar pattern. Here only the DSC curves of PEO 2.0 are shown as an example. Figure 5–2 illustrates the DSC curve of PEO 2.0 (MW=2,000,000) as (a) powder and (b) the tablet. The value of heat flow, ΔH_f , is determined by integration of the peak area. The melting point, T_m , is reported as the peak value and the onset value. The determination of the degree of crystallinity, x_c , is based on reference [34] with a heat flow value for a PEO crystal of 203 J/g and is calculated as:

$$x_c = \frac{\Delta H_f}{203} \quad (5-1)$$

The obtained value of ΔH_f and calculated x_c are given in Table 5–1. Also the onset T_m and peak T_m of melting are reported. The PEO powders have a high degree of crystallinity but the crystallinity decreases with increasing molecular weight. We also observe that the degree of crystallinity decreases by the tableting process. The reason is most likely the particle deformation during tableting as discussed above. However the results revealed no order with regards to molecular weight. A slight increase in the peak melting temperature is observed after tableting.

5.1.3 RAMAN SPECTROSCOPY

The polarized Raman spectrum of the highly crystallized PEO powder and a close-up of the lattice vibration region, 100-500 cm^{-1} , are shown in Figure 5–3. This spectrum is in excellent agreement with ref [35]. The degree of crystallinity of this powder has been determined as 0.99 and its DSC result is shown in Figure 5–3 (c). The LAM vibration mode is found at 280 cm^{-1} as a sharp and strong band. The assignments of the other bands of the highly crystallized PEO powder are given in Table 5–2 based on ref [35].

Table 5-1 Thermal properties of the PEO samples

<i>Form</i>	<u>PEO 0.1</u>		<u>PEO 0.6</u>		<u>PEO 2.0</u>		<u>PEO 4.0</u>	
	Powder	Tablet	Powder	Tablet	Powder	Tablet	Powder	Tablet
<i>Heat Flow (J/g)</i>	201.1	174.6	184.5	168.5	183.3	175.5	168.1	168.1
<i>Initial X_c</i>	0.99	0.86	0.91	0.83	0.90	0.86	0.83	0.83
<i>T_m Onset (°C)</i>	58.8	60.3	62.6	62.2	63.1	62.9	61.6	62.2
<i>T_m Middle (°C)</i>	66.3	68.3	68.8	71.1	70.1	72.3	69.2	73.9

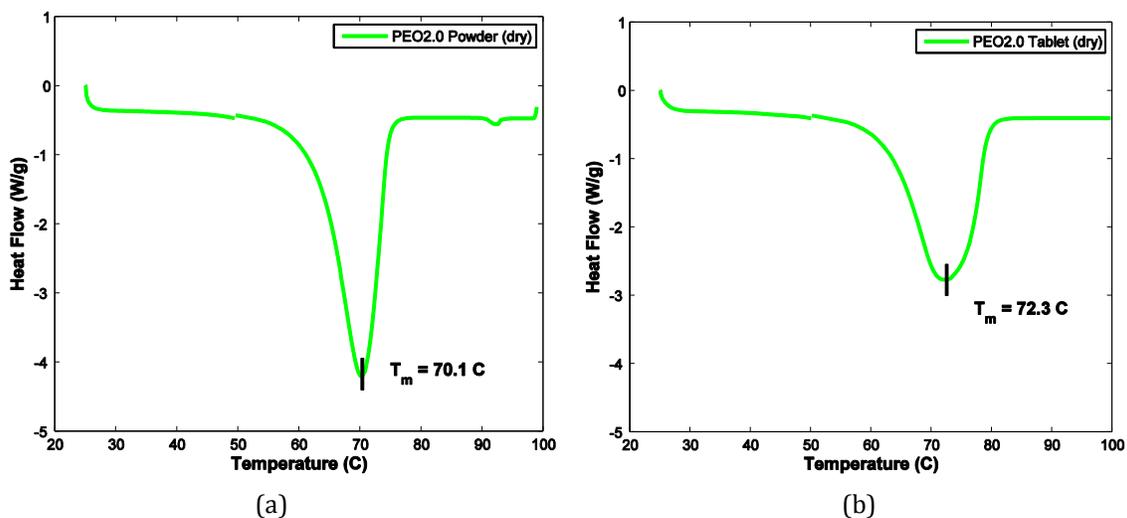
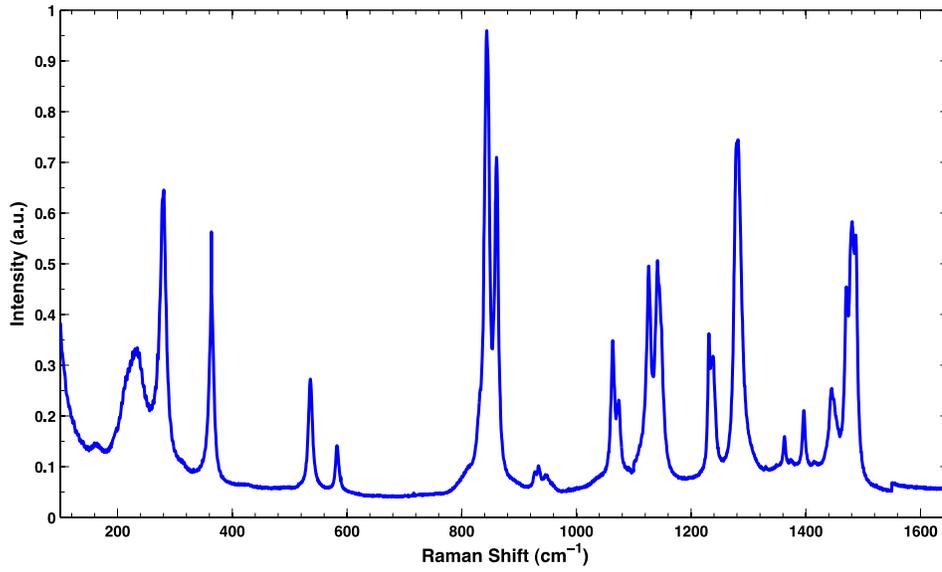
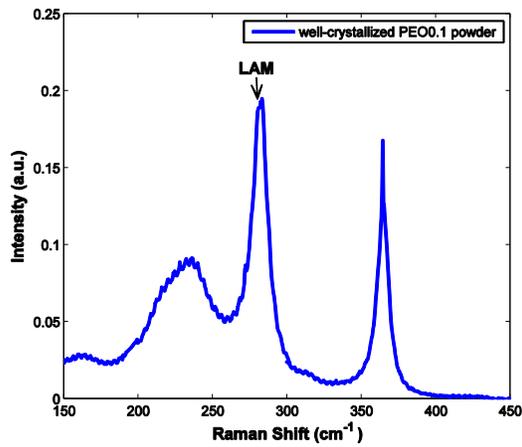


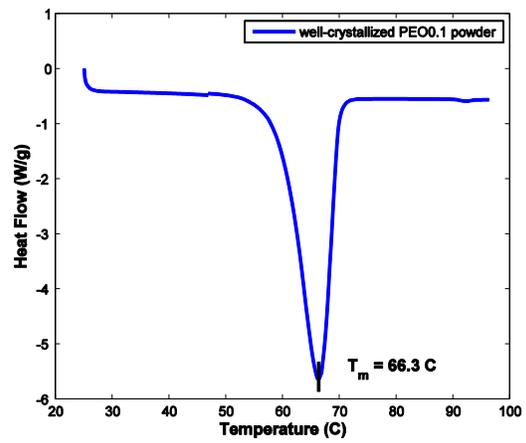
Figure 5-2 DSC curves of (a) PEO2.0 dry powder and (b) resulting compressed tablet.



(a)



(b)



(c)

Figure 5-3 Polarized Raman spectrum of (a) the PEO powder and (b) a zoom-in in the range 150-450 cm^{-1} (MW=100000, T=25 $^{\circ}\text{C}$), obtained by LabRAM spectroscopy. The corresponding DSC curve is shown in (c).

Table 5-2 Assignment of Raman bands of PEO (MW=100000, T=25°C) in the frequency range 100 - 1650 cm⁻¹ for the highly crystallized sample. The assignments are based on the work of Yoshihara et al [35]. The conventional notations used are interpreted as follows; Band intensities: w (weak); m (moderate); s (strong). Band width: sh (sharp). Mode assignments: r (rocking); t (torsion); v (stretching); ω (wagging). The assignment subscripts a and s refer the asymmetric and symmetric vibrations respectively.

Raman Shift (cm ⁻¹) in Crystalline PEO	Assignment
280s	LAM
844vs	γ (CH ₂)
862m	γ (CH ₂) _s v (COC) _s
948w	γ (CH ₂) _s v (COC) _a
936w	amorphous
1065m	γ (CH ₂) _a v (COC) _s
1075sh	γ (CH ₂) _s v (COC) _s
1127m	v (COC) _s
1143m	v (COC) _a
1234m	γ (CH ₂) _a
1283vs	γ (CH ₂) _s γ (CH ₂) _a
1363w	ω (CH ₂) _s γ (CC)
1397w	ω (CH ₂) _s v (CC)
1445m	δ (CH ₂) _s
1471sh	δ (CH ₂) _a
1487s	δ (CH ₂) _s

Table 5-3 Frequencies and bandwidths of the semi-crystalline PEO powders and the tablets. Data obtained from curve fitting

Form	PEO 0.1		PEO 0.6		PEO 2.0		PEO 4.0	
	Powder	Tablet	Powder	Tablet	Powder	Tablet	Powder	Tablet
LAM frequency (cm ⁻¹)	279	279	279	279	279	279	279	279
Bandwidth	5.2	6.7	7.2	7.1	5.0	5.3	5.4	5.6

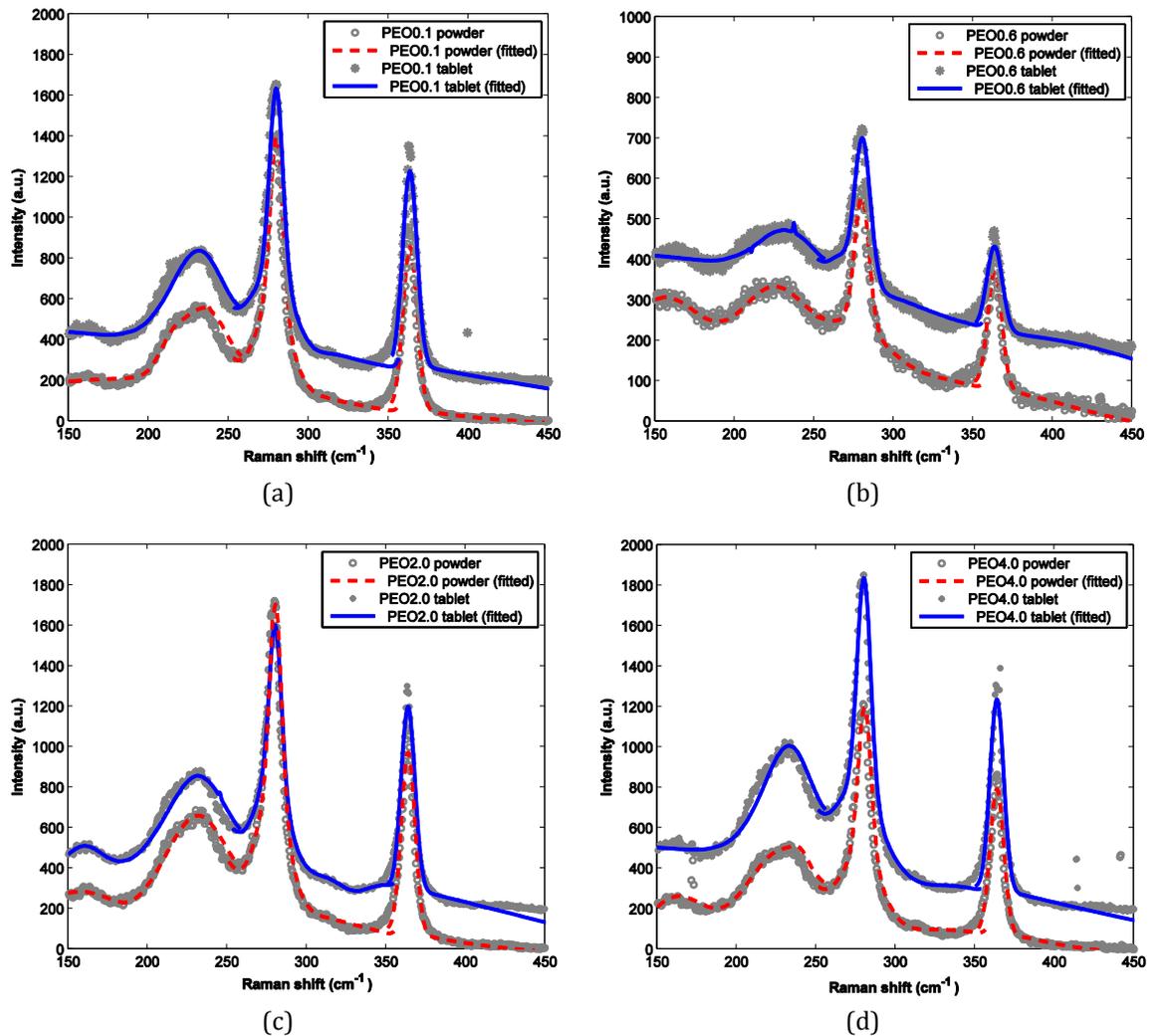


Figure 5-4 Polarized Raman spectra of PEO 0.1 (a), PEO 0.6 (b), PEO 2.0 (c) and PEO 4.0 (d) in form of powder (circle marker and dash line) and tablet (star marker and solid line), obtained by LabRAM spectroscopy. The data of the tablets have been an offset for clarity. The solid curves are a fitted multi-Gaussian model. The values of peak frequency and band width are obtained from the fitting.

The Raman analysis is focused on the low-frequency region where the LAM band appears (150-450 cm^{-1}). Figure 5-4 shows the polarized Raman spectra of PEO in form of powders and tablets for the different molecular weights obtained by Raman microscopy. A background of the spectra has been subtracted and the curves are fitted by a multi-Gaussian model. The values of peak frequency and band width are obtained from this curve fitting. The values of the frequency and bandwidth of the LAM band are presented in Table 5-3

The LAM band of all the powders and tablets is found at the same frequency, 279 cm^{-1} , and it appears sharp and strong. That indicates the same chain arrangement of all samples in the crystalline state. For PEO 0.1 the powder and its compressed tablet have different crystallinity (see Table 5-1) and the band widths measured are 5.2 and 6.7 cm^{-1} respectively. The increasing band width indicates that the polymer chains are less ordered, which agrees with the results from DSC. For the other samples this correlation cannot be observed. Possibly, the difference in crystallinity between powder and tablet is smaller and the variance in the width is less. The accuracy of determining the crystallinity from DSC should be also considered as a matter which can affect the result. In addition, during tableting, the crystalline and amorphous part may not distribute homogeneously. The tested samples are cut off from edge of the tablet where the DSC shows different crystallinity from the center.

5.2 HYDRATION OF A PEO TABLET

In this section the hydration process and Raman analysis of hydrated tablets are discussed. The PEO tablets were hydrated in different relative humidity. After equilibrium was reached, the tablets were taken out to normal atmosphere and the DSC or Raman experiments were performed immediately to minimize dehydration.

Figure 5-5 shows the water content (W_w) of the hydrated PEO tablets determined by TGA as a function of relative humidity (RH). Up to 60% RH the water uptake is low, whereas it increases rapidly for higher relative humidity. Figure 5-6 shows the water uptake as a function of molecular weight (MW) for 59% RH. It can be seen that the tablets with lower molecular weight tend to absorb slightly more water. The water content and the crystallinity of the hydrated tablets at different relative humidity are given in Table 5-4. No correlation is found between the water content in the tablet and the crystallinity. This observation is basically in agreement with the ref [33]. In hydrated PEO, water molecules tend to bond to the ether oxygen atom and the end group, which may cause the breakdown of crystals and the chain to become more flexible. Water molecules form hydrogen bonds from the surface, trying to saturate the polymer chain as the water penetrate slowly to the inside. One reason why such a trend is not observed may be due to the high packing density of the compressed tablet which makes the water penetration more difficult. There is also the possibility that the dehydration of the surface occurs immediately when it is taken out and exposed to the air before the measurements.

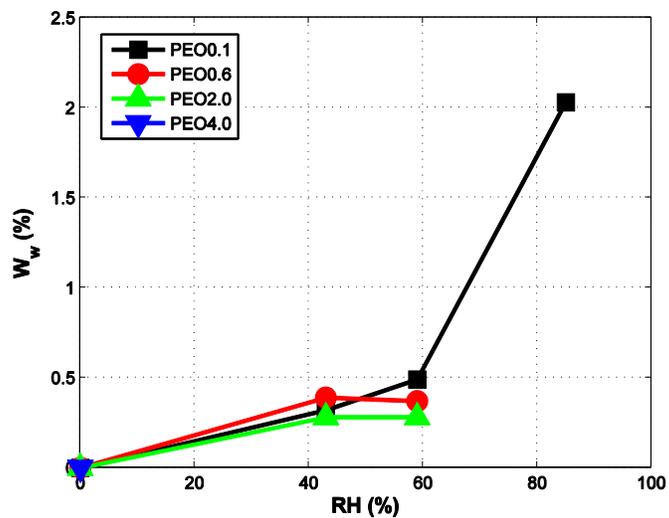


Figure 5-5 Water content as a function of the relative humidity (RH).

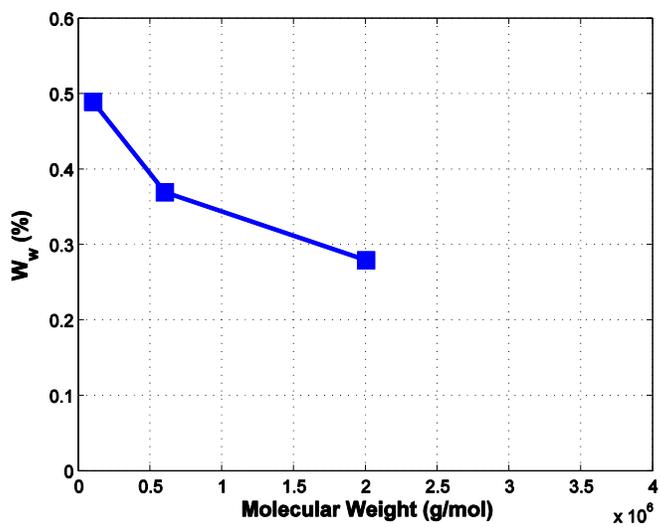


Figure 5-6 Water content as a function of molecular weight (MW) at 59% RH.

Figure 5–7 shows the polarized Raman spectrum of the hydrated PEO tablets (MW=100,000) with water concentrations of 0.18% w/w and 1.4% w/w (determined by TGA), where the hydration environments are 11% and 85% RH respectively. With increasing relative humidity in the environment, the water content in the tablets is expected to increase. As the water concentration in tablets increases the degree of crystallinity should decrease and therefore corresponding changes in the Raman spectra are expected. However, no significant changes can be observed neither in the position nor the shape of the LAM band.

After hydration, the water concentrations in the tablets only increase slightly, less than the increase in ref [26]. The PEO used in ref [26] is the same material as in our work, PEO 0.1, but the sample was prepared by melt-extrusion and molded into 1 mm thick film. The hot-extrusion and thin film form may increase the capability of absorbing water in controlled environment compared to direct compression in our work. With less water content in tablets, the decrease in crystallinity is not significant either.

As crystals melt, the sharp LAM band should be replaced by the broad D-LAM band. However, due to the very small changes in crystallinity, the shift and broadening of the LAM band are hard to observe. As shown in Table 5–5, the bandwidth is only slightly broadened in the hydrated tablets compared to that in the dry tablets. This can be due to a small increase in chain mobility because of the melting of crystals and the overall average concentration of gauche-bond with increasing water content [24], reflecting that the conformation of the chains becomes more disordered.

Table 5-4 Water content and crystallinity of tablets equilibrated at different relative humidity.

RH (%)	PEO 0.1 Tablet		PEO 0.6 Tablet		PEO 2.0 Tablet		PEO 4.0 Tablet	
	W_w (% by wt)	x_c	W_w (% by wt)	x_c	W_w (% by wt)	x_c	W_w (% by wt)	x_c
0	0	0.86	0	0.83	0	0.86	0	0.83
11	0.18	0.83	0.34	0.84	0.21	0.83	-	-
43	0.32	0.89	0.39	0.86	0.34	0.79	-	-
59	0.49	0.90	0.37	0.85	0.34	0.86	-	-
85	1.40	0.82	1.57	0.82	2.22	0.76	-	-

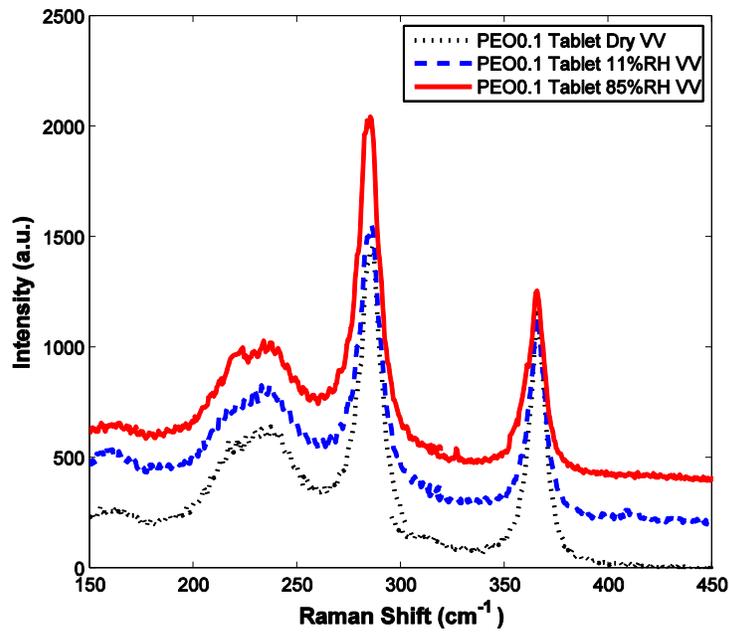


Figure 5-7 Polarized Raman spectra (LabRAM) of PEO 0.1 (MW=100,000) dry tablet (dot line) and hydrated tablets in 11% (dash line) and 85% (solid line) RH environments. The curves have been added offsets for clarity.

Table 5-5 Frequencies and bandwidths of dry and hydrated tablets. Data obtained from curve fitting.

	LAM frequency (cm ⁻¹), λ	Bandwidth, ω
PEO 0.1 (solid line) dry tablet	279	5.0
PEO 0.1 hydrated in 11% RH	279	5.4
PEO 0.1 hydrated in 85% RH	279	5.3

5.3 IN-SITU MONITORING OF HYDRATION OF A PEO TABLET

Figure 5–8 shows the polarized Raman spectra recorded during the hydration of a PEO tablet immersed in water during 35 minutes. As the water concentration in the tablet increases, the peaks at 230 cm^{-1} and 363 cm^{-1} decrease in intensity and the sharp LAM peak at 280 cm^{-1} is gradually replaced by a much broader D-LAM band from 200 to 400 cm^{-1} . The bands at 535 cm^{-1} and 580 cm^{-1} also decrease during hydration, but the intensity between these two peaks increases. These two peaks were not found in the diluted solution in a previous study of low molecular weight PEO (MW=600) [20, 22]. One reason may be due to the high molecular weight of the polymer which is not fully extended in the gel phase, causing the differences in the Raman spectra.

From these observations it is possible to quantitatively represent the decrease of crystallinity by following the changes in the Raman spectra. In addition to the LAM band, the sharp bands at 363 , 535 , and 580 cm^{-1} are clear signatures of the crystalline state. Of these bands the 363 cm^{-1} has the least interference with spectral components corresponding to amorphous PEO.

The spectra in Figure 5–8 are shown individually in Figure 5–9. These spectra represent the different average hydration times. For instance, Figure 5–9 (b) is presented as integration time T , 180s, and hydration time t , 3 min, which indicates that the spectrum is an average signal of a 180s measurement and the tablet has been immersed in water for 3 minutes when the measurement starts.

To quantitatively follow the hydration, the band at 363 cm^{-1} provides the most favorable conditions, due to less interference with the signature of the amorphous phase. The intensity of the band is determined by fitting the range from 353 to 373 cm^{-1} with a Gaussian band shape, shown in Figure 5–9. In Figure 5–10 the area of the peak at 363 cm^{-1} is plotted against the average hydration time, $t_{av}=t+T/2$, and also the corresponding crystallinities are plotted on right y-axis. The data are normalized to the crystallinity of the dry tablet PEO 2.0, see Table 5–1 and Figure 5–10 and fitted by two exponential functions and plotted in linear and log-linear scales. Here we assume that the changes of scattering intensity are linear to the changes in crystallinity. The curve shows a rapid decrease in intensity corresponding to the crystallinity in the initial hydration phase and for a longer time a relative slow decrease is observed. This turning point of hydration rate is found at 7 minutes. This result is in basic agreement with the previous studies on the dissolution mechanism of semi-crystalline poly (vinyl alcohol) (PVA) [16].

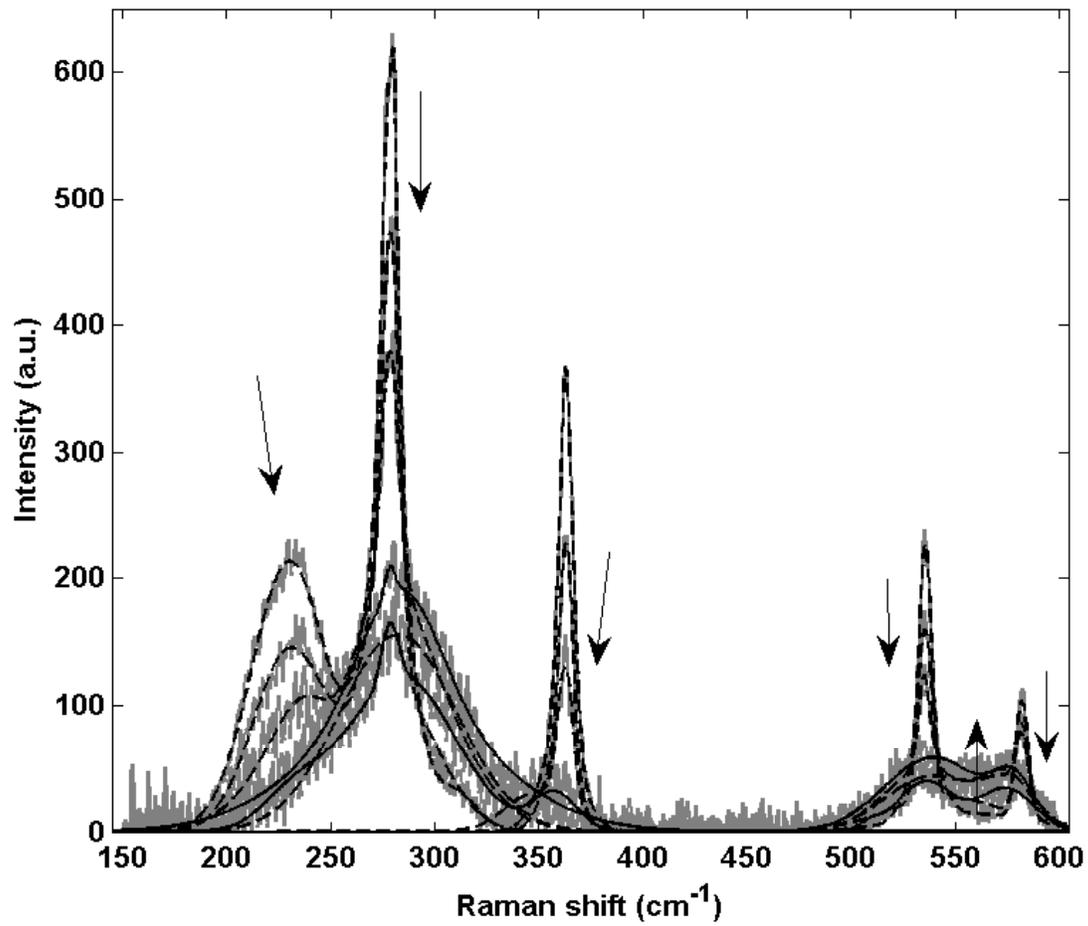


Figure 5-8 Hydration process of PEO tablet monitored by LabRAM spectroscopy, raw data (solid line) and fitted data (dash line). The trends of peak changing are marked by arrows.

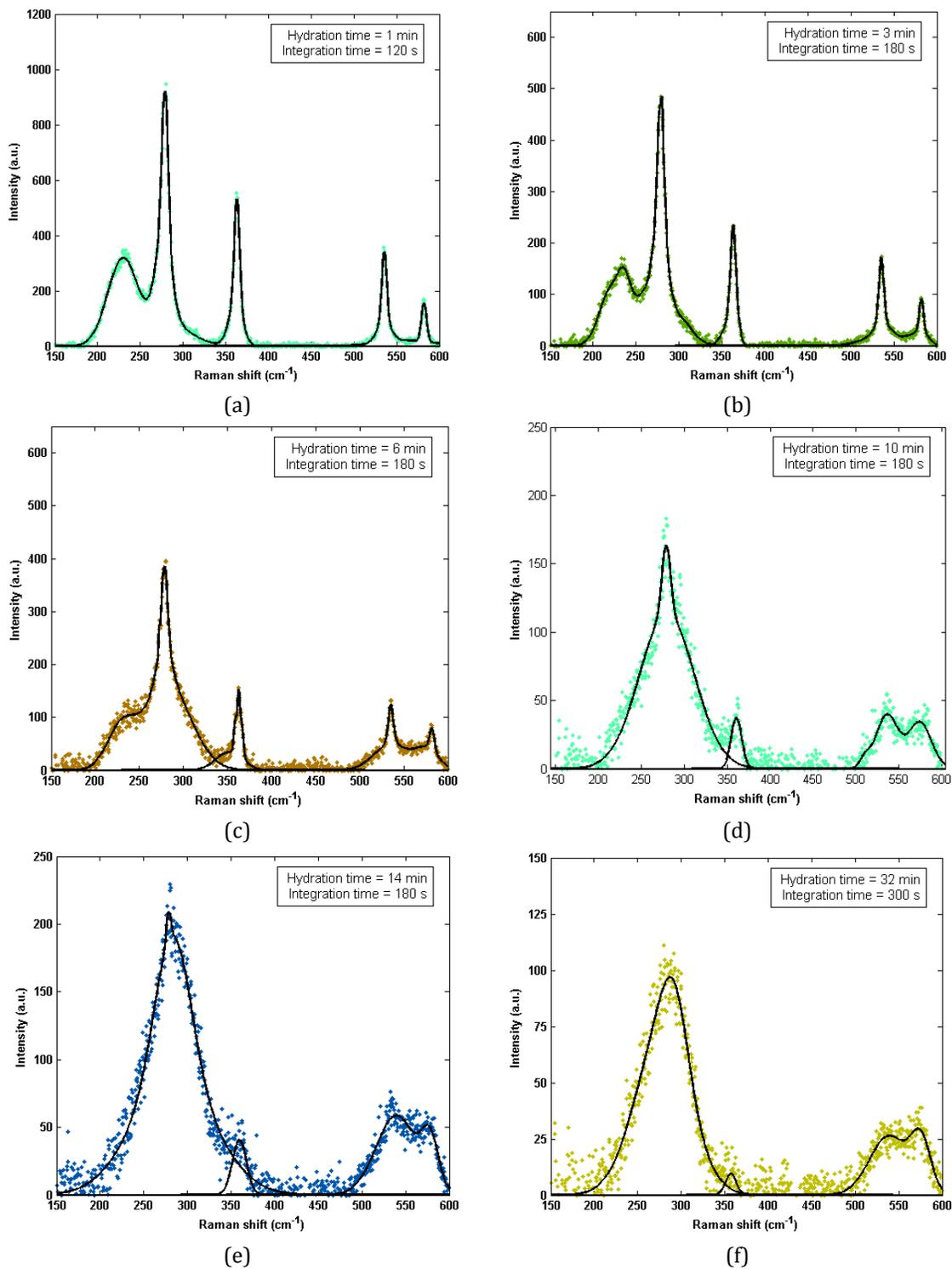
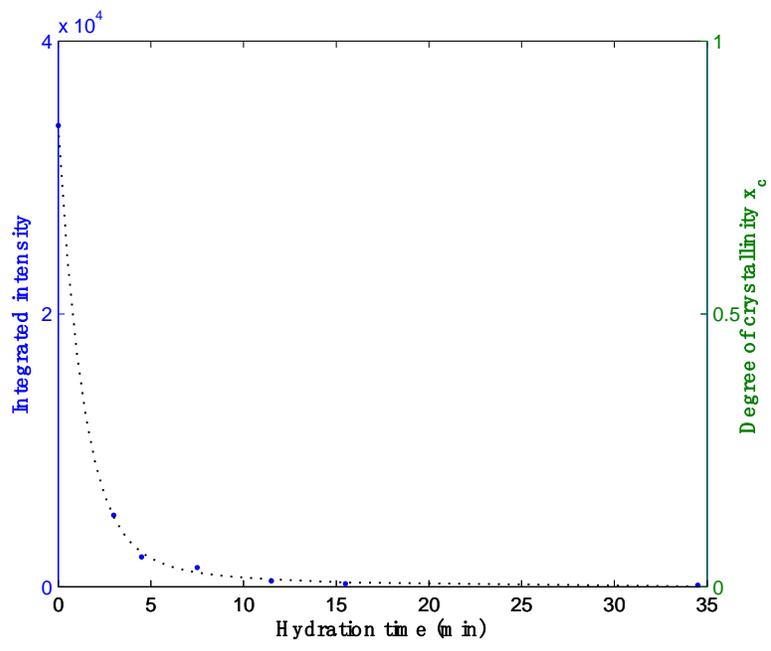
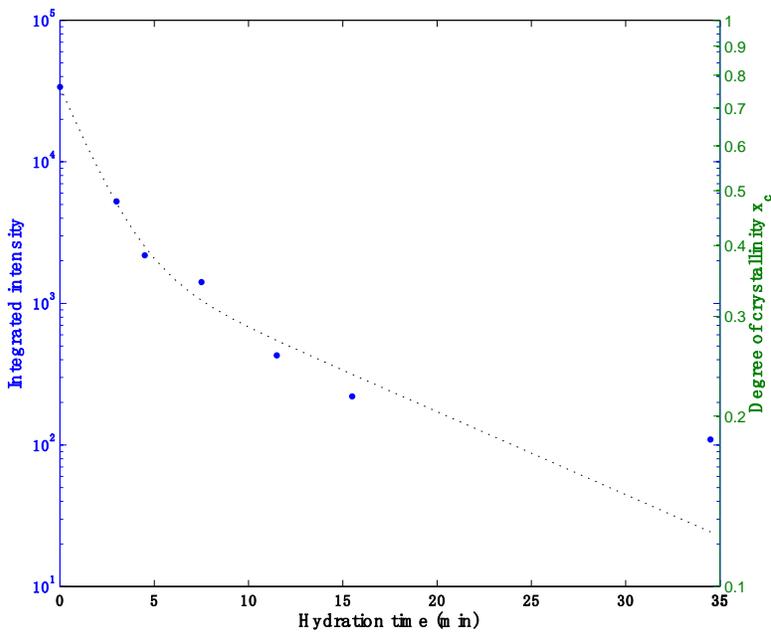


Figure 5-9 Polarized Raman spectra of PEO tablet (MW=2*10⁶) hydrating by immersing in water, raw data (dot) and fitted curve (solid line). The background has been subtracted and data are fitted by multi-Gaussian model.



(a)



(b)

Figure 5-10 Integration area of peak from 353 to 373 cm⁻¹ plotted against average hydration time, $t_{av}=t+T/2$, fitted by (a) exponential function (dot line) and (b) curves plotted on log-linear scale.

CHAPTER 6 CONCLUDING REMARKS

The present work has shown how the data obtained by Raman spectroscopy, DSC, and TGA enables us to understand the influence on the properties of PEO by tableting process and the dissolution profile of a PEO tablet. After tableting a slight increase of melting point and slight decrease of the degree of crystallinity are found compared to the PEO powders. The Raman analysis for the dry PEO powders and tablets shows a slight broadening of the LAM band at 280 cm^{-1} for the tablets, reflecting the decrease of the degree of crystallinity.

For the hydration of tablets, up to 60% RH the water uptake is very low. Low molecular weight tablets tend to absorb more water. No correlation is found between the water content in the tablet and the degree of crystallinity. The Raman analysis again observed a slight increase in bandwidth for LAM band at 280 cm^{-1} for the hydrated tablets compared to the dry one. Due to the lack of data, it is hard to build any correlation between the bandwidth and the degree of crystallinity for the dry and hydrated tablets containing small amounts of water (before the gel phase is formed). However by increasing the water concentration in the tablet, the decrease of the degree of crystallinity and the broadening of the LAM band are observed.

By Raman measurements of a PEO tablet immersed in water, the dissolution profile of the crystals was determined by integrating the peak at 363 cm^{-1} . This peak has the least interference with the spectral components corresponding to the amorphous phase of PEO. A rapid decrease in the intensity of the 363 cm^{-1} band, reflecting the degree of crystallinity, decrease is observed during initial hydration. Overall the decrease in the degree of crystallinity follows an exponential decay. The LAM to D-LAM band transition is also recorded by Raman spectroscopy. However the LAM and D-LAM band are not suitable to follow the dissolution profile due to its complex spectral components.

CHAPTER 7 ACKNOWLEDGMENTS

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