# REFERENCES

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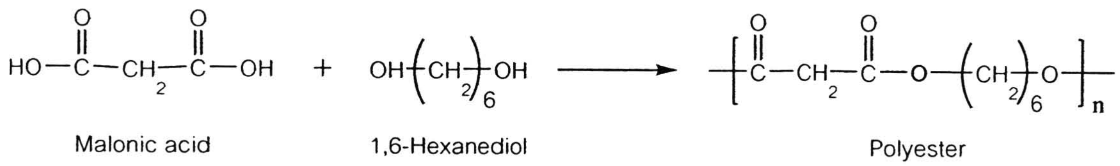
# APPENDIX

# APPENDIX A Calculations

**Calculation of the amounts of mPEG, diol and dicid monomer used in the syntheses of mPEG-polyester copolymer**

1. The molecular weight of mPEG block used is 2,000 g/mol
2. The expected molecular weight of polyester block is 5,000 g/mol
3. The overall molecular weight of mPEG- polyester copolymer is 7,000 g/mol



1. Weight of 1,6-hexane diol and malonic acid needed

   Weight of repeating unit of polyester $C_9H_{14}O_4$ = 186 g/mol

$$X_n = (5{,}000/186)\ \text{g/mol}$$

$$X_n = 26.88 \approx 27\ \text{unit}$$

Carother's equation : $X_n = (1+r) / (1-r)$

When r is ratio of 1,6-hexane diol : malonic acid

$$27 = (1+r) / (1-r)$$

$$27 - 27r = 1 + r$$

$$r = 26/28 = 1/1.07$$

Then 1,6-hexane diol 1 mol : malonic acid 1.07 mol

Assumed $n_1$ is mol of malonic acid

$n_2$ is mol of 1,6-hexane diol

Then $n_1/ n_2 = 1.07$

$$n_1 = 1.07\, n_2 \qquad — 1$$

From $n = g/mw$ or $g = n \times mw$

Molecular weight of malonic acid ($C_3H_4O_4$) 104 g/mol

Molecular weight of 1,6-hexane diol ($C_6H_{14}O_2$) 118 g/mol

The expected weight of polyester 5.00 g

$$5.00 = 104\, n_1 + 118\, n_2 \text{ — } 2$$

From (1) $n_1 = 1.07\, n_2$

$$5.00 = 104\,(1.07 n_2) + 118 n_2$$

$$5.00 = 229.28\, n_2$$

$$n_2 = 0.022$$

$\therefore$ 1,6-hexane diol $0.022 \times 118 = 2.60$ g

Substitute $n_2 = 0.022$ in equation 2

$$5.00 = (104 \times n_1) + (118 \times 0.022)$$

$$n_1 = 0.033$$

$\therefore$ malonic acid $0.023 \times 104 = 2.39$ g

Overall of polyester $2.60 + 2.39 = 4.99$ g

2. **Calculation of the amounts of mPEG** needed

Ratio of polyester:mPEG = 1 : 1

Weight of 5,000 g/mol polyester = 4.99 g

Mol of polyester $= 4.99$ g / 5,000 g/mol

$= 9.98 \times 10^{-4}$ mol

mPEG $= 9.98 \times 10^{-4}$ mol

Targeted weight of mPEG = 2,000 g/mol

mPEG $= 2{,}000 \times (9.98 \times 10^{-4})$ g

$= 1.996 \approx 2.00$ g

**Calculation of the weights of ferrous chloride ($FeCl_24H_2O$) and ferric chloride ($FeCl_3$) used in the preparation of magnetite nanoparticles**

1. Molecular weight of ferrous chloride ($FeCl_2 \cdot 4H_2O$) is 198.71 g/mol
2. Molecular weight of ferric chloride ($FeCl_3$) is 162.20 g/mol

The chemcial equation for the sysnthesis of magnetite ($Fe_3O_4$):

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \longrightarrow Fe_3O_4 + 4H_2O \qquad \text{...A-2}$$

**Step 1. Calculate the weight of $FeCl_2 \cdot 4H_2O$ and mole of $Fe^{2+}$ needed**

There is 55.85 g of $Fe^{2+}$ in 198.71 g of $FeCl_2 \cdot 4H_2O$. If we want 1.00 g of $Fe^{2+}$, the weight of $FeCl_2 \cdot 4H_2O$ could be calculated as follow:

$$\text{Weight of } FeCl_2 \cdot 4H_2O = \frac{(198.71\text{ g})(1.00\text{ g})}{55.85\text{ g}} = 3.50\text{ g}$$

$$\text{Therefore, the mole of } Fe^{2+} = \frac{1.00\text{ g}}{55.85\text{ g/mol}} = 1.80\times10^{-2}\text{ mol}$$

**Step 2. Calculate the weight of $FeCl_3$**

From the equation A-2, the molar ratio of $Fe^{3+}$: $Fe^{2+}$ is 2 : 1. Then, the mole and weight of $FeCl_3$ could be calculated as follow:

$$\text{Mole of } Fe^{3+} = 1.80\times10^{-2}\text{ mol} \times 2 = 3.60\times10^{-2}\text{ mol}$$

$$\text{Weight of } Fe^{3+} = 3.60\times10^{-2}\text{ mol} \times 55.85\text{ g/mol} = 2.00\text{ g}$$

There is 55.85 g of $Fe^{3+}$ in 162.20 g of $FeCl_3$. If we want 2.00 g of $Fe^{3+}$, the weight of $FeCl_3$ needed could be calculated as follow:

$$\text{Weight of } FeCl_3 \text{ needed} = \frac{(162.20\text{ g})(2.00\text{ g})}{55.85\text{ g}} = 5.80\text{ g}$$

Therefore, to synthesize magnetite nanoparticles using 2:1 molar ratio of $Fe^{3+}$: $Fe^{2+}$, 3.55 g $FeCl_2 \cdot 4H_2O$ and 5.80 g $FeCl_3$ was required in the reaction, respectively.

**Determination of magnetite concentrations Via atomic absorption spectroscopy (AAS) technique**

**Preparation of magnetite standard solutions for the calibration curve**

$2.50 \times 10^{-2}$ g of $FeSO_4$ was used for preparation of a 100.00 ml stock solution in deionized water. Various concentration solutions, 1.00, 2.00, 3.00, 4.00, and 5.00 ppm, were prepared using 1.00, 2.00, 3.00, 4.00, and 5.00 ml, respectively, of the stock solution and adjusted the volume to 50.00 ml. The exact concentrations of each solution were analyzed by AAS technique.

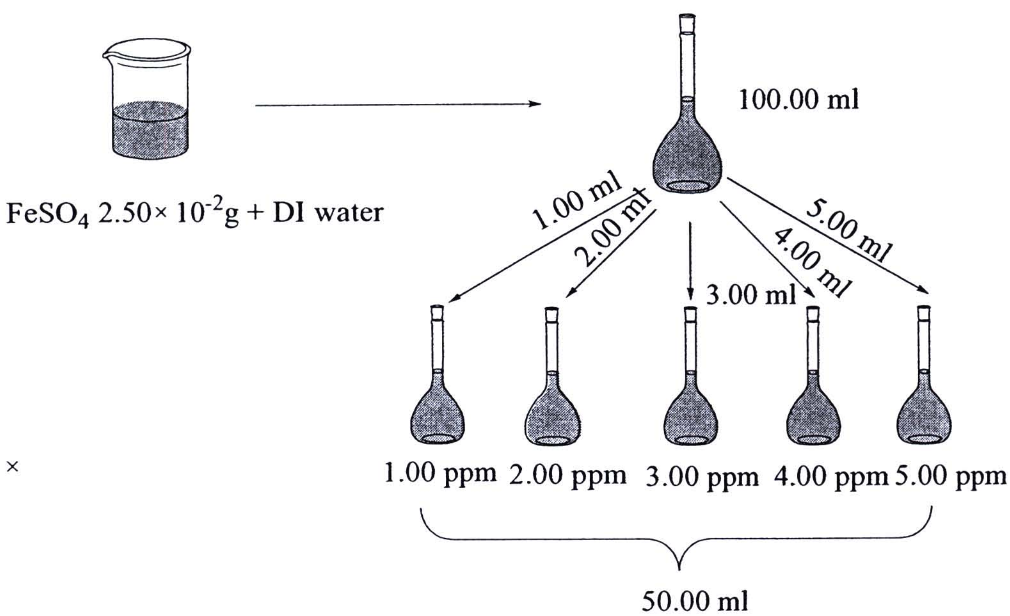



**Figure 47 Preparation scheme of magnetite standard solutions**

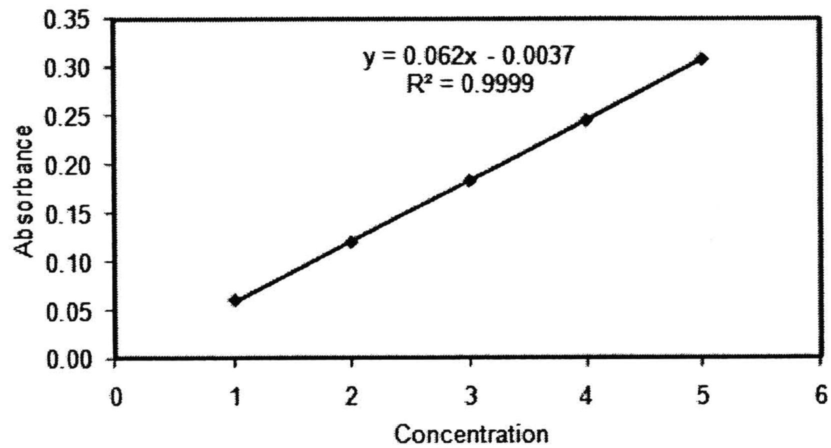



**Figure 48 Calibration curve of $FeSO_4$with various concentration solutions**

**Magnetite nanoaparticles in the form of aqueous dispersions**

1. Digestion method

A 0.10 ml solution of mPEG-polyester copolymer-stabilized magnetite nanoparticles was digested with a 5.00 ml 70.00% nitric acid solution under heating environment until there was no observable precipitate of magnetite particles. 5.00 ml perchloric acid was then pored into the solution and the solution color changed from yellow to clear appearance. Volume of the solution was adjusted to 50.00 ml before analyzed by AAS technique.

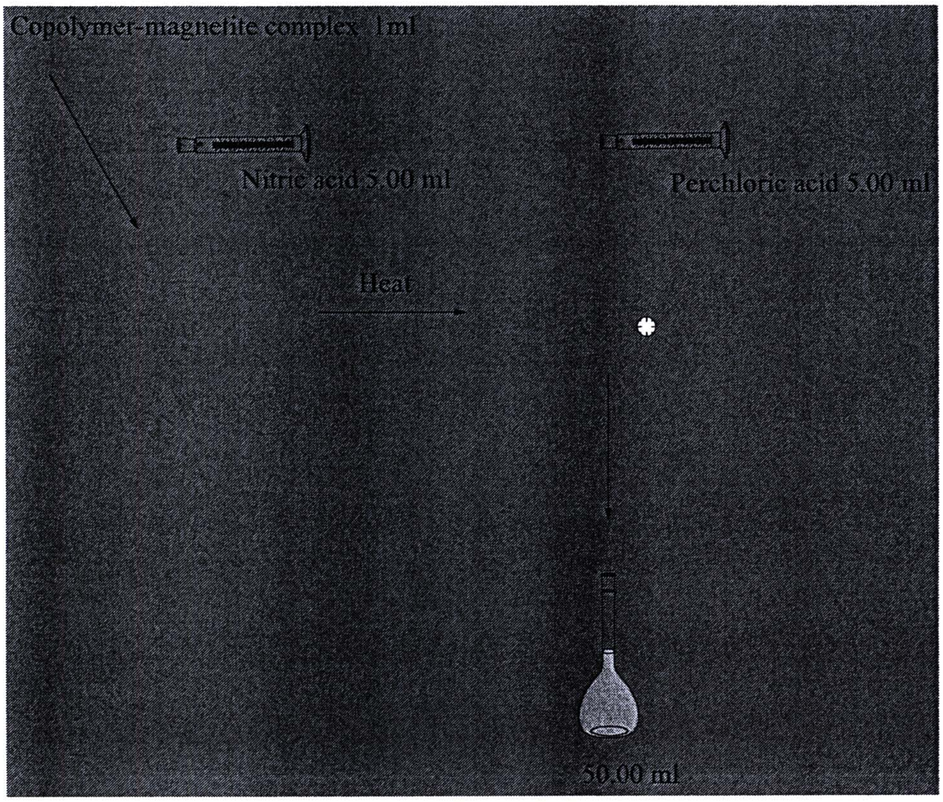



**Figure 49 Digestion of magnetite dispersions to determine the concentrations of dispersible magnetite in aqueous dispersions**

2. Determination of the concentrations of dispersible magnetite in aqueous dispersions

A 1.00 ml of 1.00% w/v magnetite stabilized with mPEG-polyester copolymer (Ma/He/M5) solution was decomposed as described above. The decomposed solution was diluted to 50.00 ml and analyzed *via* AAS technique. The observed concentrations of total Fe were 130.54 ppm.

Calculation of total Fe concentration:

The solution 1,000.00 ml contains total Fe = 130.54 mg

The solution 100.00 ml should contains total Fe $= \dfrac{(130.54\ \text{mg})(100.00\ \text{ml})}{1000.00\ \text{ml}}$

$= 13.05$ mg

Thus, a 1.00 ml of magnetite solution (the amount used) has Fe = 1.305 mg

= 1305 % mg/ml

= 1.30 % g/ml

Calculation of $Fe_3O_4$ concentration in the dispersion:

The molecular weight of Fe = 55.84 g/mol Fe

The formula weight of $Fe_3O_4$ = 231.48 g/mol

From the equation;

$$Fe^{2+} + 2Fe^{3+} + 8OH^{-} \longrightarrow Fe_3O_4 + 4H_2O$$

Three moles of Fe (1.00 mole of $Fe^{2+}$ and 2.00 moles of $Fe^{3+}$) result in one mole of $Fe_3O_4$

Thus, 1.30 g/ml of Fe can form $Fe_3O_4$

$$= \frac{(231.48\ g/mol)(1mol)(1.30\ g/ml)}{(55.84 g / mol)(3mol)}$$

= 5.41 g/ml

**Calculation of the molecular weight of mPEG-polyester diblock copolymer from a $^{1}$H-NMR spectrum**

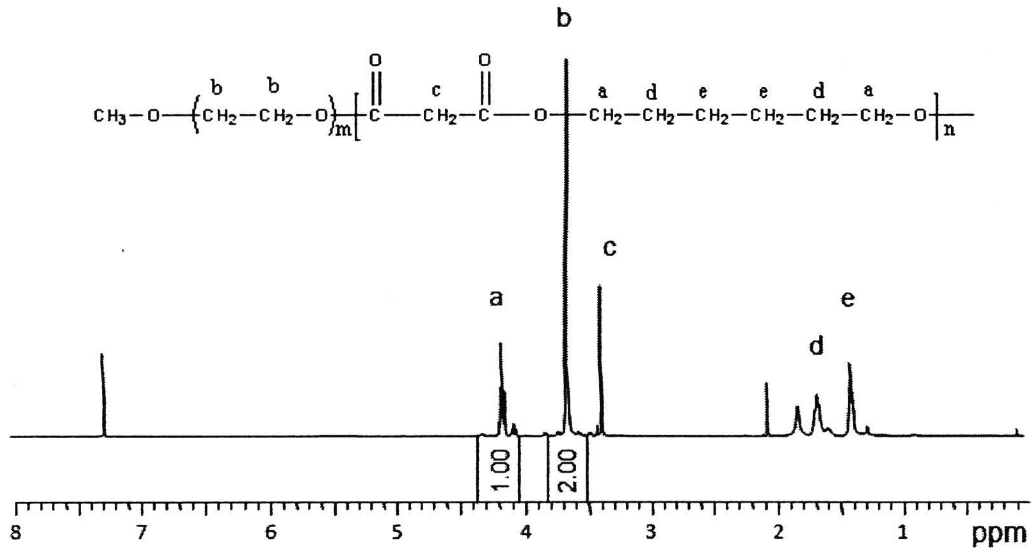



**Figure 50 A $^{1}$H NMR spectrum of Ma/He/M2**

Estimation of number of repeating units of polyester segments:

**Step 1**: Calculate number of protons in mPEG block

Molecular weight of one repeating unit of mPEG = 44.01 g/mol

Thus, the unit number of 2,000.00 g/mol mPEG should be $= \frac{2000.00 \text{ g/mol}}{44.01 \text{ g/mol}}$

= 45.45 units

One repeating unit of mPEG has 4.00 protons

Thus, the number of protons of 2,000.00 g/mol mPEG $= 45.45 \times 4.00$

= 181.8 H

From the $^{1}$H-NMR spectrum, the integration ratio of mPEG (peak *b*) = 2.0

The integration ratio of one proton $= \frac{2.0}{181.8}$

Therefore, integration ratio of one proton $= 1.1\times10^{-2}$

**Step 2**: Estimate the molecular weight of polyester segments

The integration ratio of methylene protons (peak *a*) = 1.00

Unit of polyester has 4.00 methylene protons of peak *a*

The number of repeating units of polyester $= \dfrac{1.00}{1.1 \times 10^{-2} \times 4.00}$

$= 22.73$ units

Because the molecular weight of polyester = 186 g/mol

Thus, the molecular weight of polyester block = 186 g/mol × 22.73 units

= 4,227 g/mol

There for molecular weight of mPEG-polyester = 2,000 g/mol + 4,227 g/mol

= 6,227 ~ 6,000 g/mol

**Calculation of percent of the composition in the copolymer-magnetite complex determined via Thermogravimetric Analysis (TGA) technique**

1. Bare magnetite (Percent char yield = 93%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (93/93) x100 | = 100 % |

2. Oleic acid-magnetite complex (Percent char yield = 66%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (66/93) x100 | = 71 % |
| % Oleic acid | = 100-71 | = 29 % |

(weight ratio of $Fe_3O_4$ : Oleic = 2.4 : 1)

3. 1% copolymer (Ma/He/M5)-magnetite complex (Percent char yield = 31%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (31/93) x100 | = 33 % |
| % Oleic acid | = (1x33)/2.4 | = 14 % |
| % copolymer | = 100-(33+14) | = 53 % |

4. 0.1% copolymer (Ma/He/M5)-magnetite complex (Percent char yield = 32%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (32/93) x100 | = 34 % |
| % Oleic acid | = (1x34)/2.4 | = 14 % |
| % copolymer | = 100-(34+14) | = 52 % |

5. 0.01% copolymer (Ma/He/M5)-magnetite complex (Percent char yield = 34%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (34/93) x100 | = 37% |
| % Oleic acid | = (1x37)/2.4 | = 15 % |
| % copolymer | = 100-(37+15) | = 48 % |

6. 0.001% copolymer (Ma/He/M5)-magnetite complex

(Percent char yield = 31%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (31/93) x100 | = 33 % |
| % Oleic acid | = (1x33)/2.4 | = 14 % |
| % copolymer = 100-(33+14) | | = 53 % |

7. Unsat-coated particle (Percent char yield = 27%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (27/93) x100 | = 29 % |
| % Oleic acid | = (1x29)/2.4 | = 12 % |
| % mPEG- unsaturated polyester = 100-(29+12) | | = 59 % |

8. Crosslinked-coated particle (Percent char yield = 26%)

| | | |
|---|---|---|
| % $Fe_3O_4$ | = (26/93) x100 | = 28 % |
| % Oleic acid | = (1x28)/2.4 | = 11 % |
| % mPEG- crosslinked polyester = 100-(28+11) | | = 61 % |

**Calculation of indomethacin entrapment efficiency (%EE)**

Entrapment efficiency (%EE) was determined from the following equation:

$$\%\text{Entrapment Efficiency (\%EE)} = \frac{\text{Weight of the entrapped drug in the complex}}{\text{Weight of loaded drug}} \times 100$$

**Calculation of the weight of the loaded indomethacin**

One ml of the indomethacin-THF solution (0.1 g indomethacin/ml THF) was loaded into the dispersion of copolymer-magnetite complex in water.

0.20 ml was taken and diluted 10,000 folds.

0.20 ml was then taken for UV measurement.

The observed concentration from UV was 9.92 ppm.

The prednisolone solution 1,000 ml contains prednisolone = 9.92 mg

The prednisolone solution 0.20 ml contains prednisolone $= \frac{(9.92 \text{ mg})(0.20 \text{ ml})}{1000 \text{ ml}}$

$= 1.98\times10^{-3}$ mg

Due to 10,000-time dilution, prednisolone $= 1.98\times10^{-3}\text{mg} \times 10{,}000$

$= 19.84$ mg

$= 1.98\times10^{-2}$ g

**Calculation of the entrapped drug in the complex**

An example of sat-coated particle is shown. Total volume of indomethacin-loaded particles = 6.00 ml

0.50 ml was taken and the particles were precipitated with 1.00 ml EtOH:THF solution; total volume = 1.50 ml

0.10 ml was taken and diluted 100 folds.

0.20 ml was then taken for UV measurement.

The observed concentration from UV was 13.75 ppm.

The indomethacin solution 1,000 ml contains indomethacin = 13.75 mg

The indomethacin solution 0.20 ml contains indomethacin $= \frac{(13.75\, mg)(0.20\, ml)}{1000\, ml}$

$= 2.75\times10^{-3}$ mg

Due to 100-time dilution, indomethacin $= 2.75\times10^{-3}$ mg $\times$ 100

$= 0.27$ mg

A solution 0.10 ml contains indomethacin $= 0.27$ mg

The total volume 6.00 ml contains indomethacin $= \frac{(0.27 \text{ mg})(6.00 \text{ ml})}{0.1 \text{ ml}}$

$= 16.50$ mg

$= 1.65\times10^{-2}$g

From the above equation:

$$\%EE = \frac{1.65\times10^{-2}\ \text{g}}{1.98\times10^{-2}\ g}\times100 = 83.33\ \%\text{w/w}$$

**Calculation of drug (indomethacin) loading efficiency (%DLE)**

Drug (indomethacin) loading efficiency (%DLE) was determined from the following equation:

$$\%\text{Drug Loading Efficiency } (\%\text{DLE}) = \frac{\text{Weight of entrapped drug in the complex}}{\text{Weight of nanoparticles}}$$

**Calculation of the weight of the complex**

According to AAS measurement, the sat-coated particle contains $Fe_3O_4$ nanoparticles about 0.021 % wt/v.

Solution contains $Fe_3O_4$ nanoparticles $= 2.1 \times 10^{-2}$ g

Calculation of the entrapped indomethacin was illustrated in the above example of %EE. The value was $1.65\times10^{-2}$ g of the loaded indomethacin.

Thus,

$$\%\text{DLE} = \frac{(1.65\times10^{-2}\text{ g})(100)}{2.1\times10^{-2}\text{ g}} = 78.57\ \%\ \text{w/w}$$

**Calculation of drug (indomethacin) release efficiency (%drug release)**

**Calculation of the entrapped drug in the complex**

According to the entrapped drug in the complex, the sat-coated particle in water 5.00 ml contains drug about $1.65 \times 10^{-2}$ g. A 5.00 ml from the entrapped drug in the complex was dialyzed in a phosphate buffer solution pH 7.45

Calculation of drug (indomethacin) releasing efficiency (%drug release)

A 5.00 ml from the drug loaded solution was dialyzed in a 300.00 ml phosphate buffer solution pH 7.45.

A 5.00 ml from 300.00 ml solution was collected.

A 0.20 ml from the collected was diluted 2 times

0.20 ml was then taken for UV measurement.
The observed concentration from UV was 12.64 ppm.

The concentration analyzed at the ending hour.

The indomethacin solution 1,000 ml contains indomethacin = 12.64 mg

The indomethacin solution 0.20 ml contains indomethacin $= \dfrac{(12.64\text{ mg})(0.20\text{ ml})}{1000.00\text{ ml}}$

$= 2.53\times10^{-3}$ mg

Due to 2-time dilution, indomethacin $= 2.53\times10^{-3}$ mg $\times$ 2

$= 5.05\times10^{-3}$ mg

A solution 0.20 ml contains indomethacin $= 5.05\times10^{-3}$ mg

Thus, a solution 5.00 ml contains indomethacin $= \dfrac{(5.05\times10^{-3}\text{ mg})(5.00\text{ ml})}{0.20\text{ ml}}$

$= 1.26\times10^{-1}$ mg

A solution 300.00 ml contains drug matter $= \frac{(1.26\times10^{-1}\ \text{mg})(300\ \text{ml})}{5.00\ \text{ml}}$

$= 7.58$ mg

or $= 7.58\times10^{-3}$ g

Calculation of the entrapped indomethacin was illustrated in the above example of %EE. The value was $1.65\times10^{-2}$ g of the loaded indomethacin.

Thus, the %drug release is.

$$\%\ \text{Drug Release} = \frac{(7.58\times10^{-3}\,\text{g})\times(100)}{1.65\times10^{-2}\,\text{g}}$$

$$= 45.93\ \%\text{w/w}$$

**APPENDIX B Spectra FT-IR of mPEG-polyester coplymers**

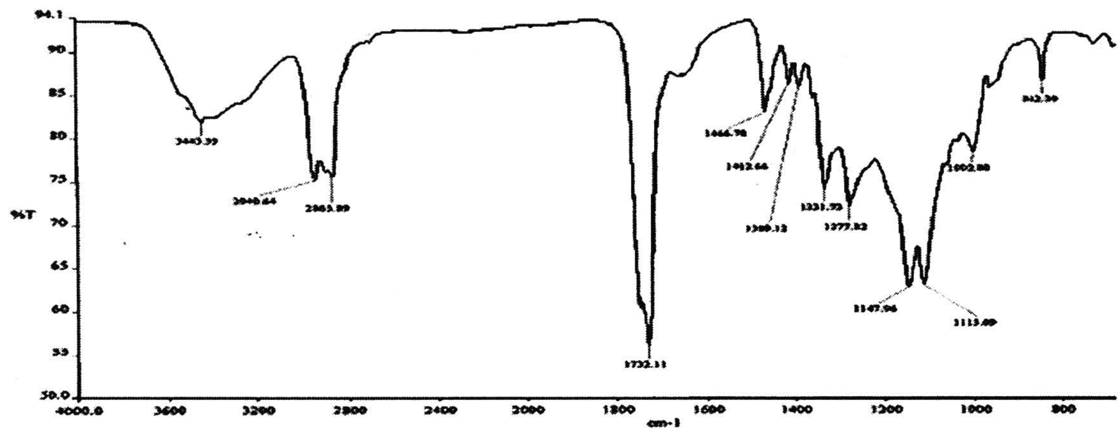


**Figure 51 FT-IR spectrum of mPEG-polyester copolymer Ma/He/M2**

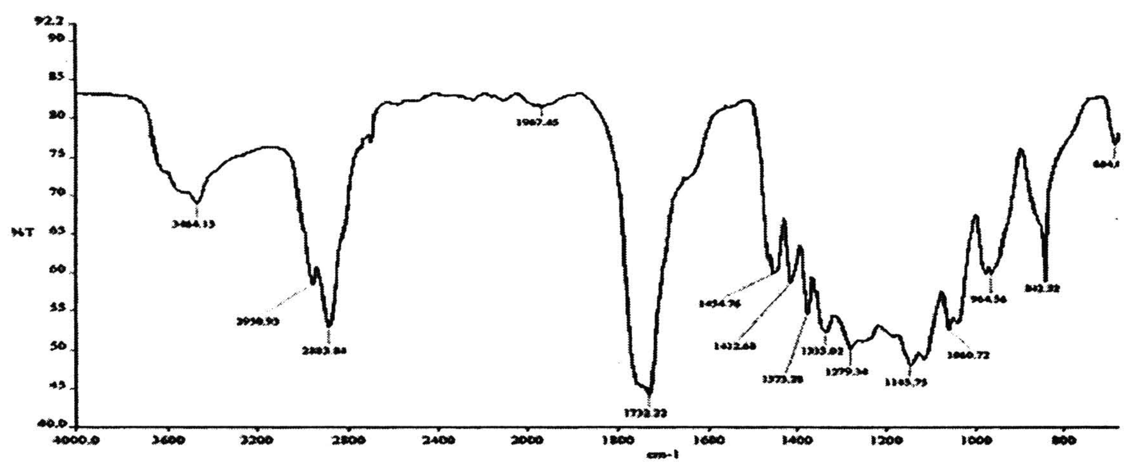


**Figure 52 FT-IR spectrum of mPEG-polyester copolymer Ma/Et/M2**

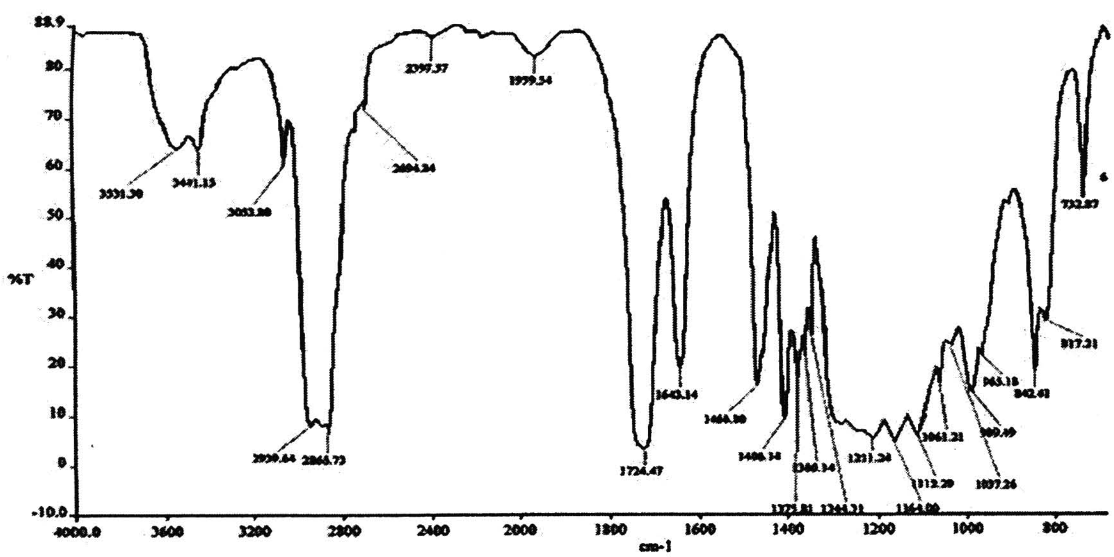



Figure 53 FT-IR spectrum of mPEG-polyester copolymer Me/He/M2

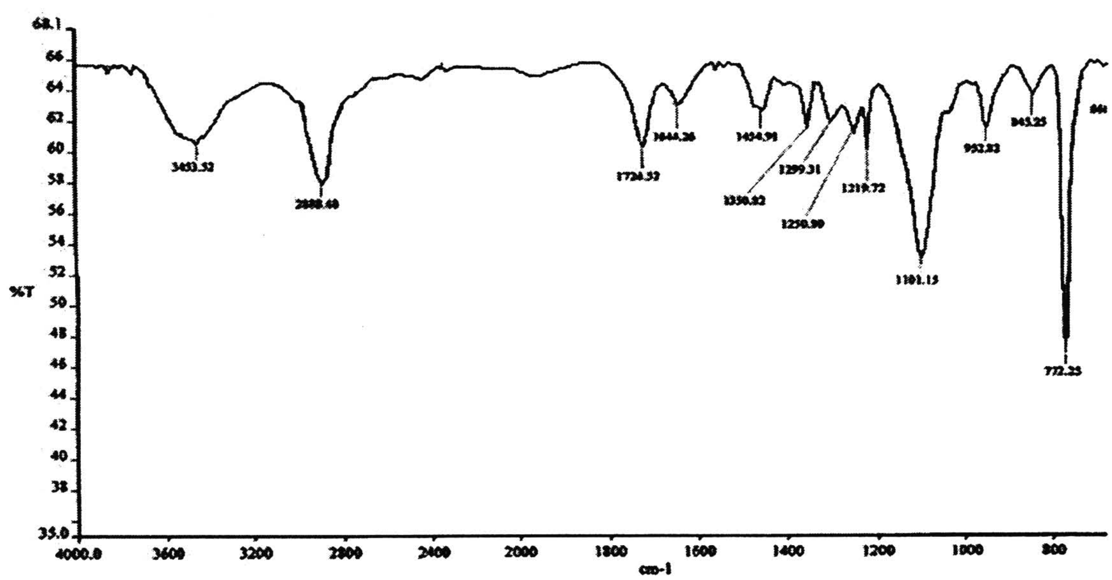



Figure 54 FT-IR spectrum of mPEG-polyester copolymer Me/Et/M2

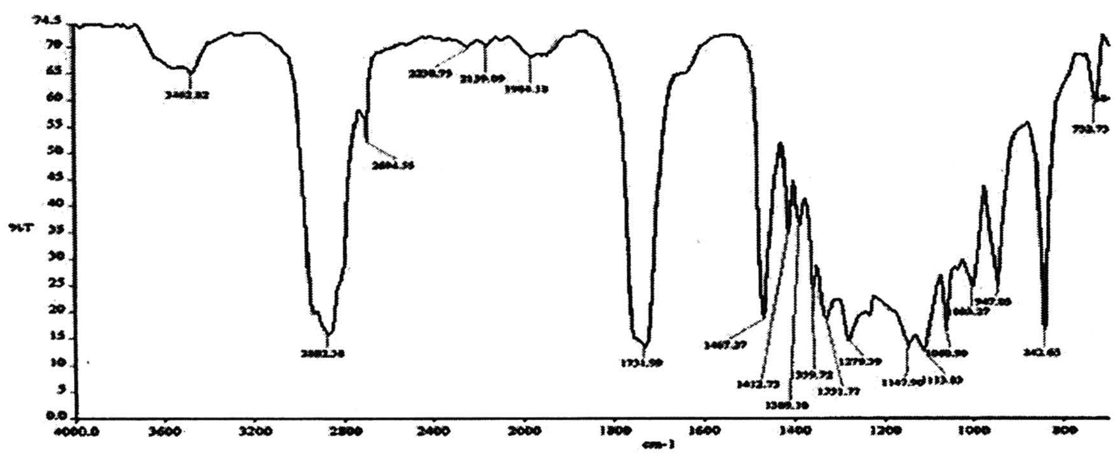



**Figure 55 FT-IR spectrum of mPEG-polyester copolymer Ma/He/M5**

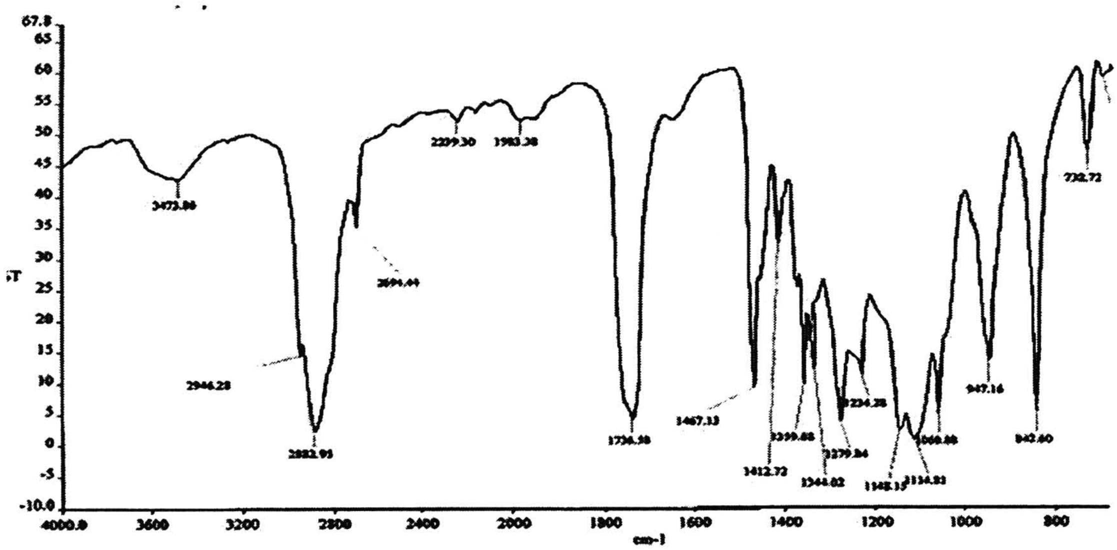



**Figure 56 FT-IR spectrum of mPEG-polyester copolymer Ma/Et/M5**

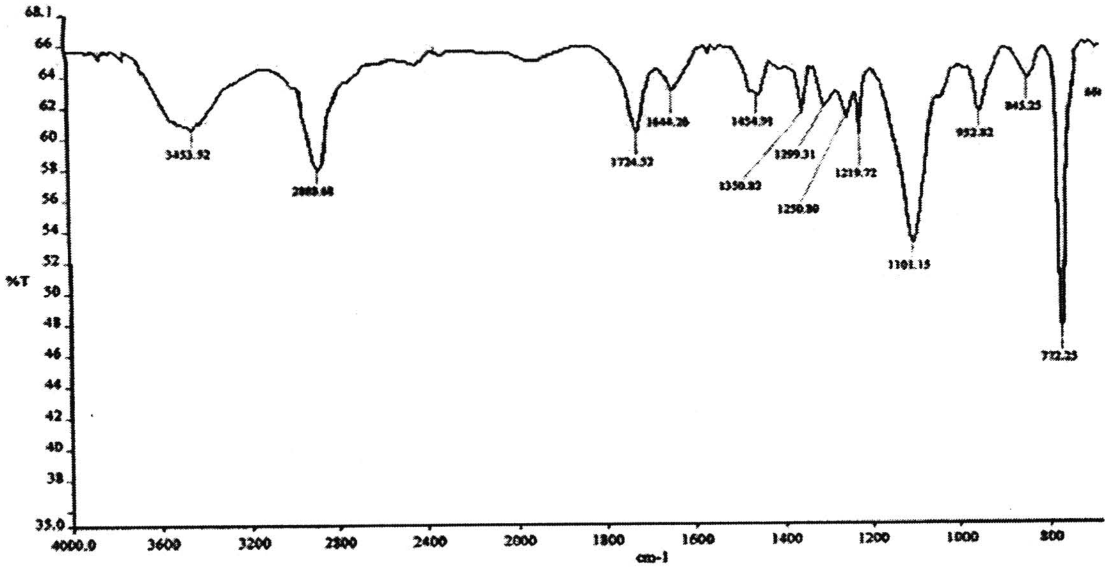


Figure 57 FT-IR spectrum of mPEG-polyester copolymer Me/He/M5

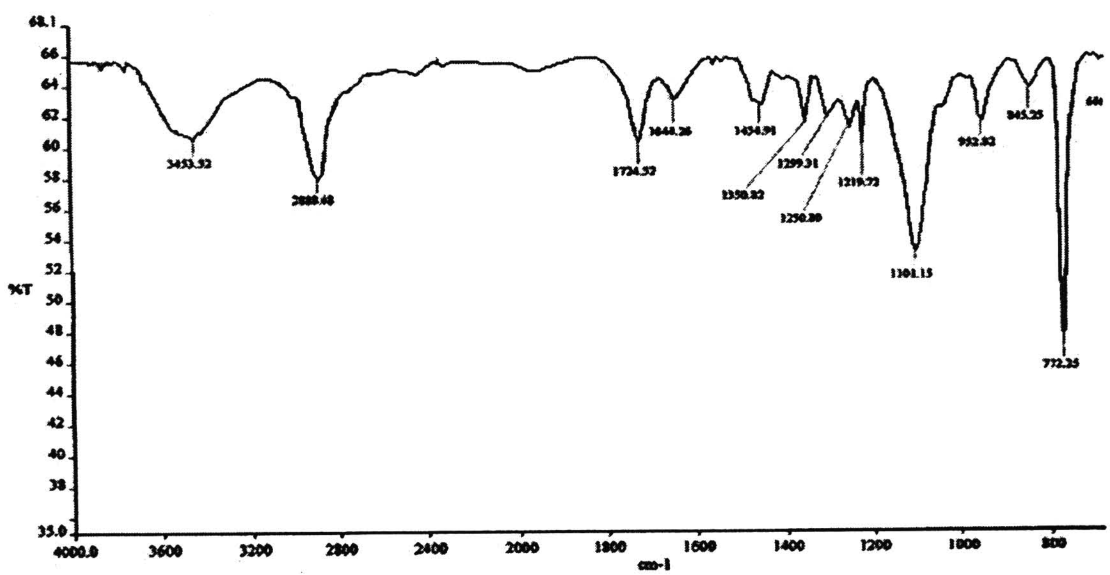


Figure 58 FT-IR spectrum of mPEG-polyester copolymer Me/Et/M5

**Spectra ¹H NMR of mPEG-polyester coplymer**

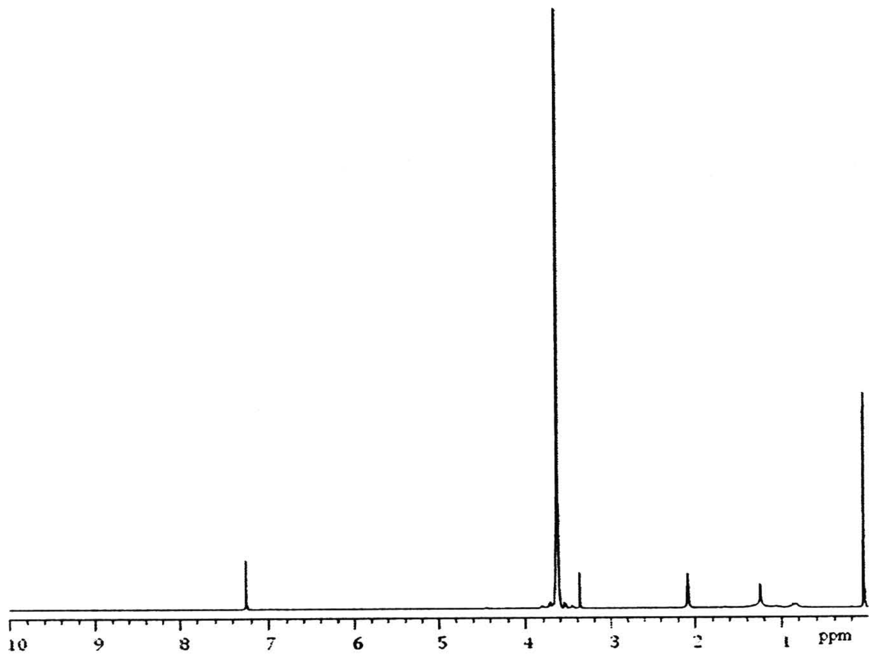



**Figure 59 ¹H NMR spectrum of mPEG 2K**

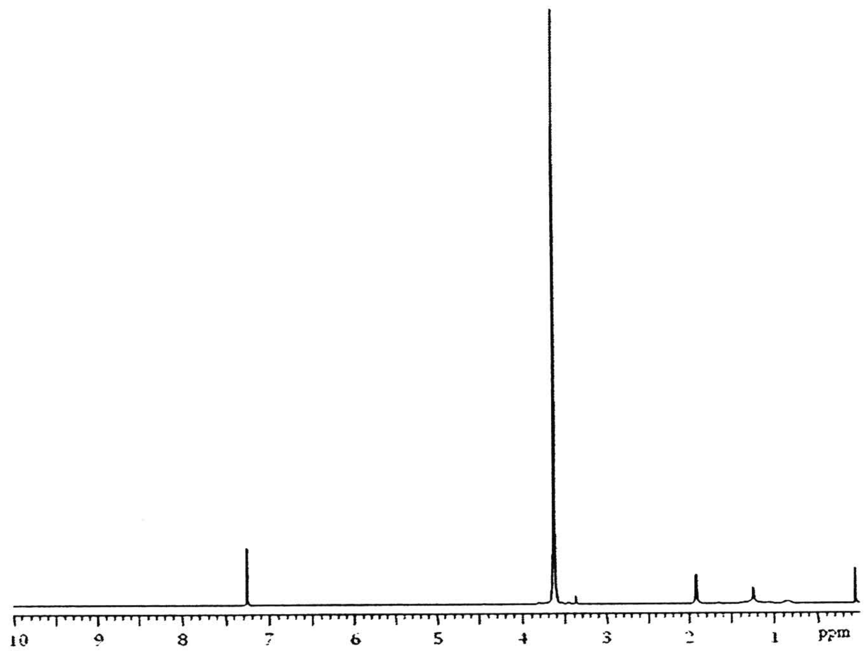



**Figure 60 ¹H NMR spectrum of mPEG 5K**

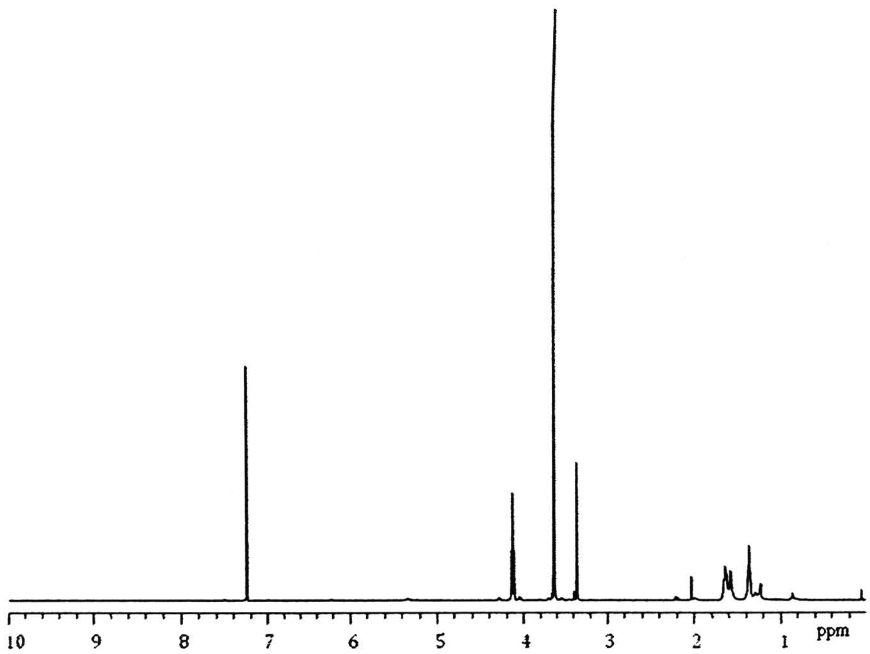



**Figure 61 ¹H NMR spectrum of mPEG-polyestercopolymer Ma/He/M2**

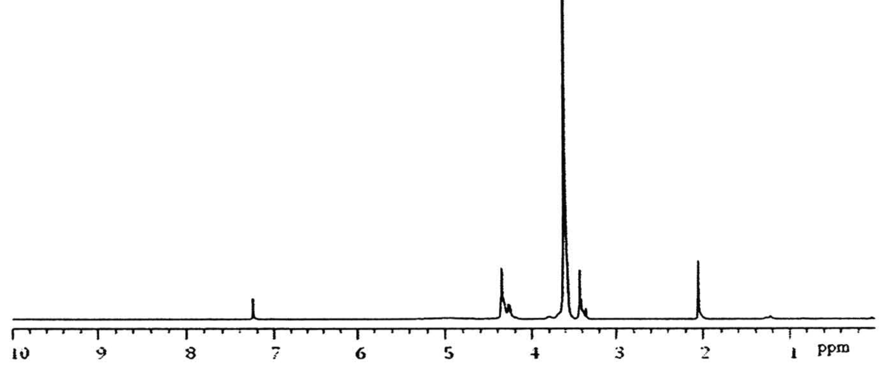



**Figure 62 ¹H NMR spectrum of mPEG-polyester copolymer Ma/Et/M2**

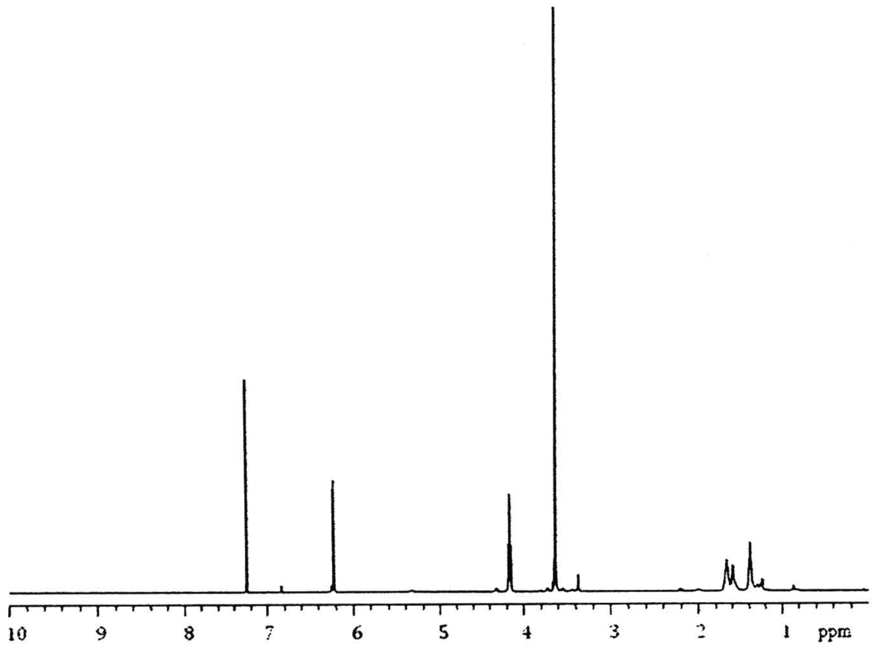



**Figure 63** $^{1}$**H NMR spectrum of mPEG-polyester copolymer Me/He/M2**

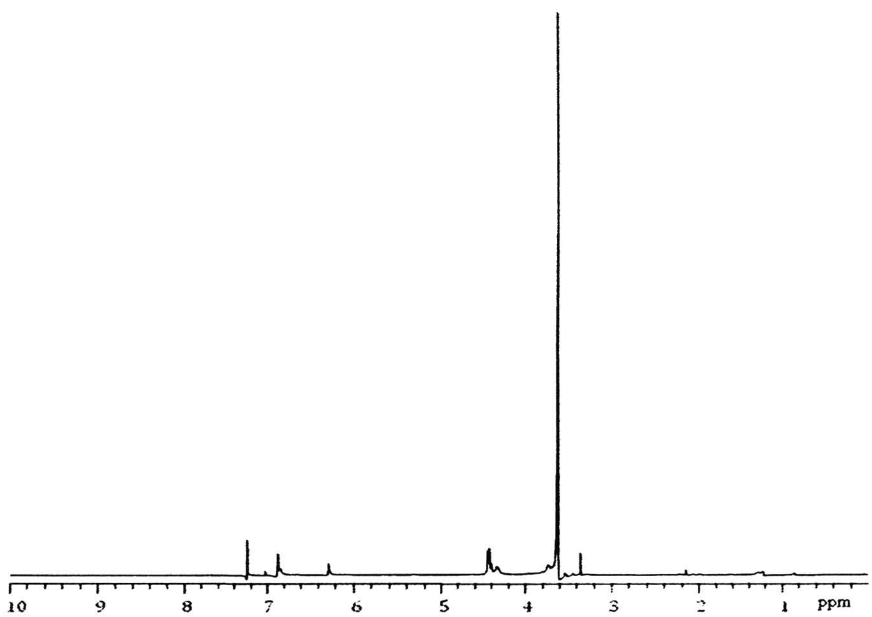



**Figure 64** $^{1}$**H NMR spectrum of mPEG-polyester copolymer Me/Et/M2**

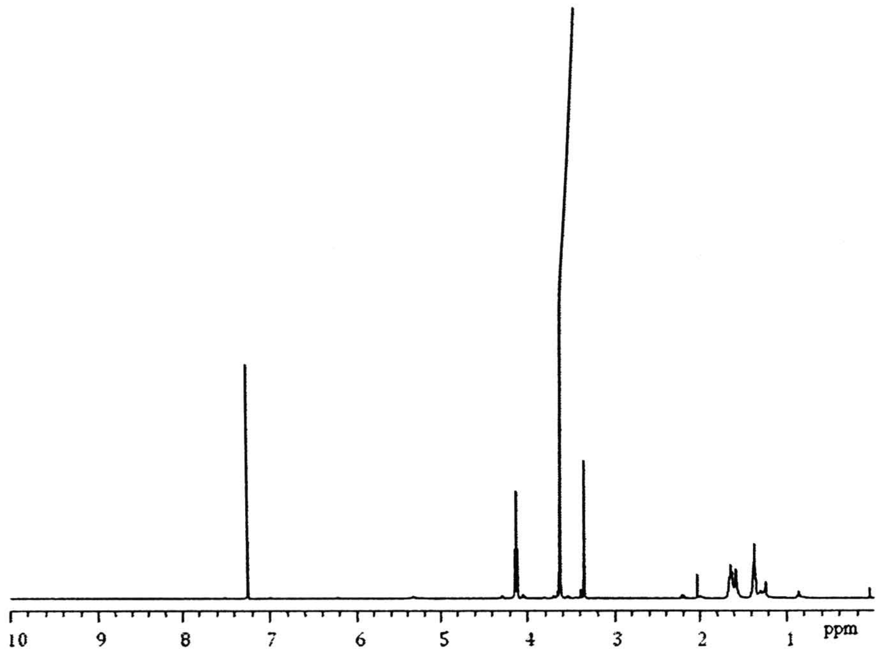



**Figure 65 $^{1}$H NMR spectrum of mPEG-polyester copolymer Ma/He/M5**

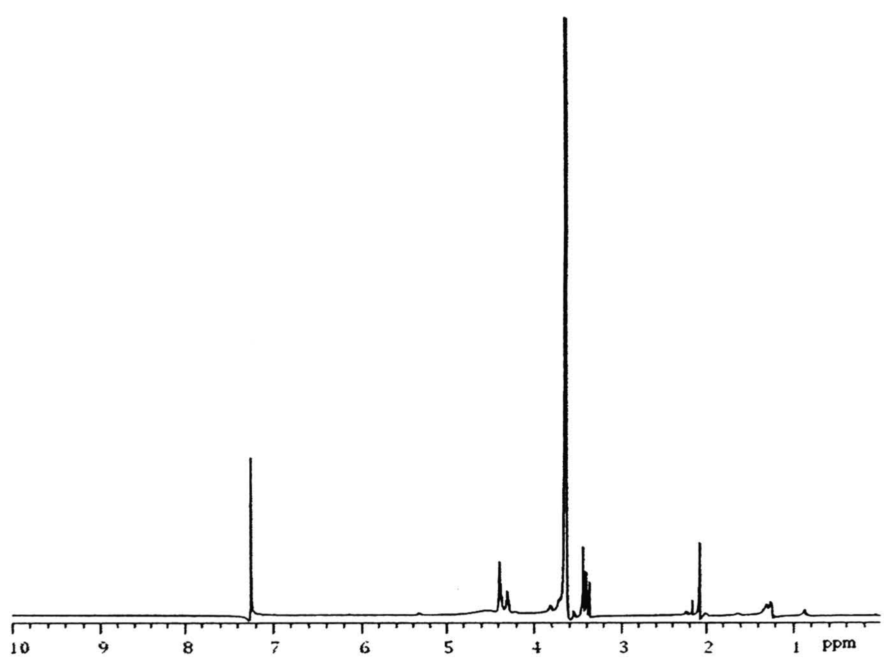



**Figure 66 $^{1}$H NMR spectrum of mPEG-polyester copolymer Ma/Et/M5**

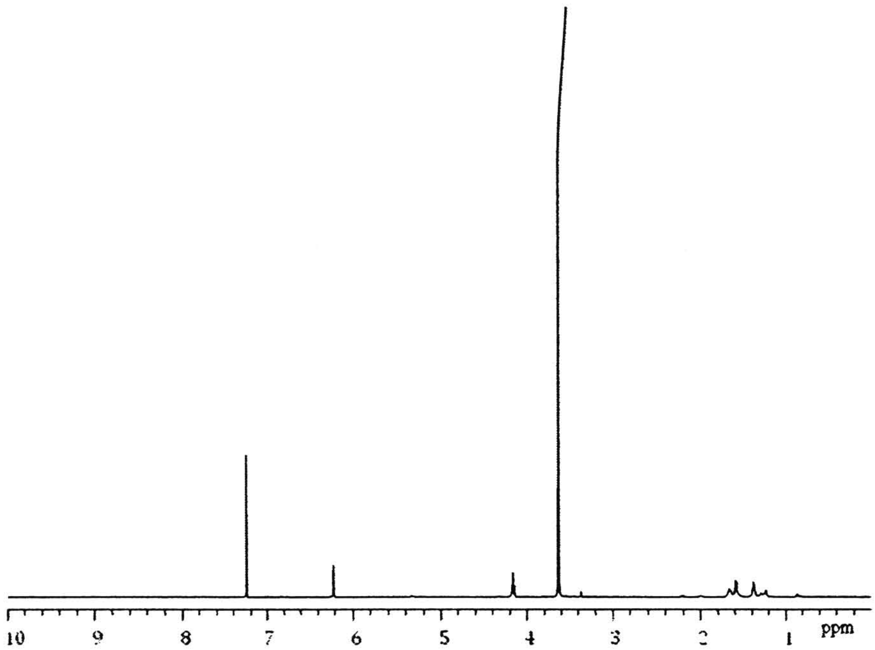



**Figure 67 $^{1}$H NMR spectrum of mPEG-polyester copolymer Me/He/M5**

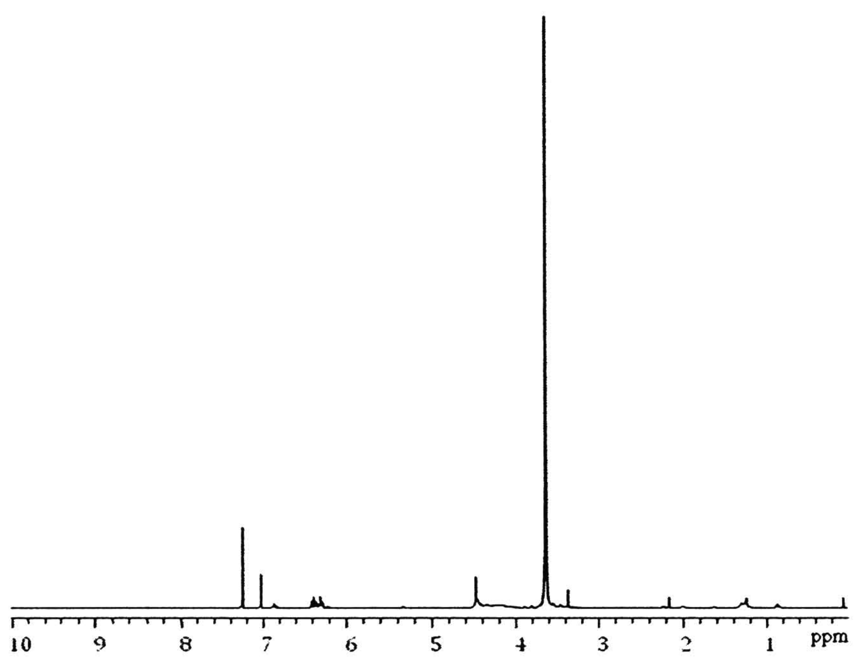



**Figure 68 $^{1}$H NMR spectrum of mPEG-polyester copolymer Me/Et/M5**

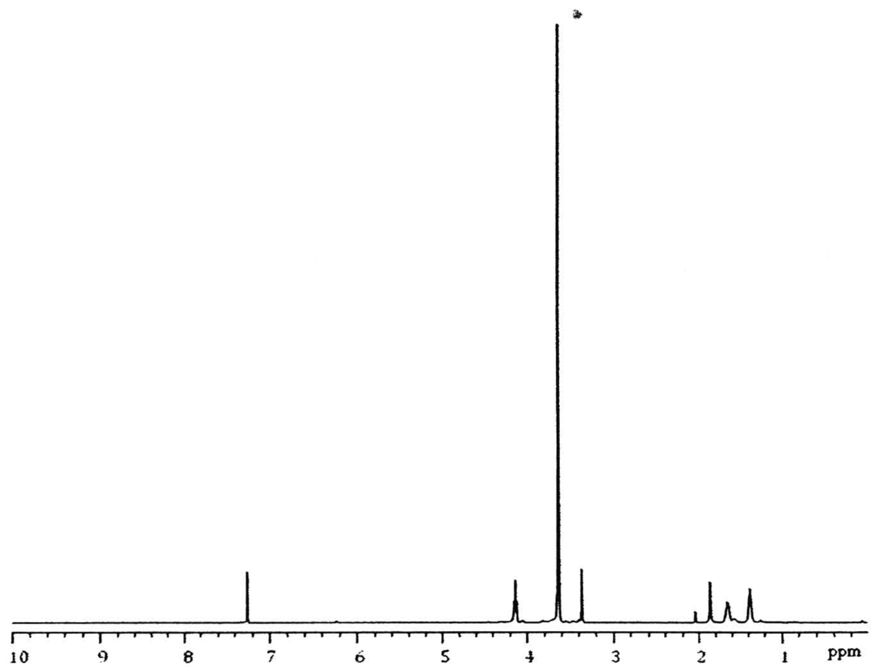



**Figure 69 $^{1}$H NMR spectrum of mPEG-polyester copolymer unsat-coated particle**

**Calibration curve of Indomethacin**

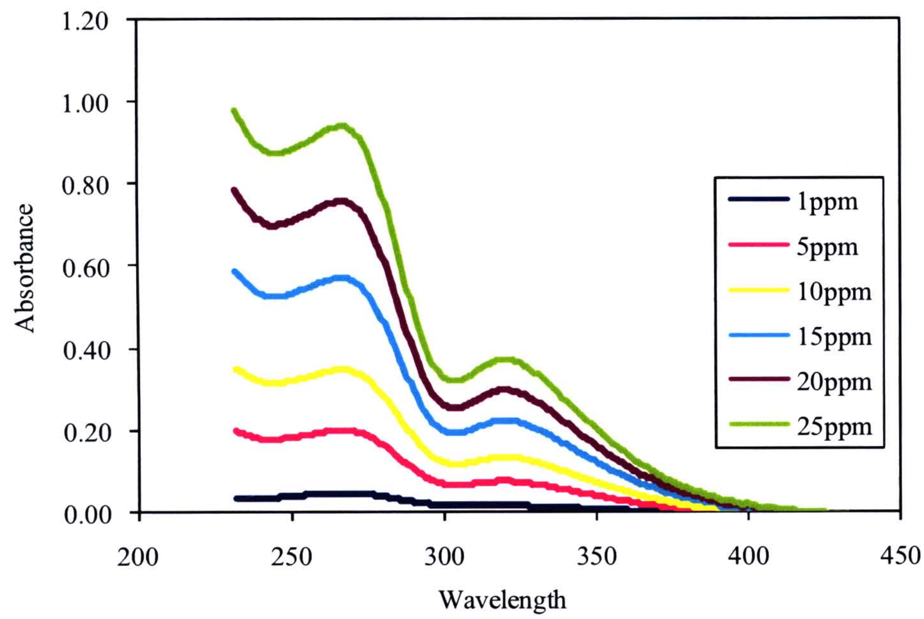



**Figure 70 UV spectra of Indomethacin**

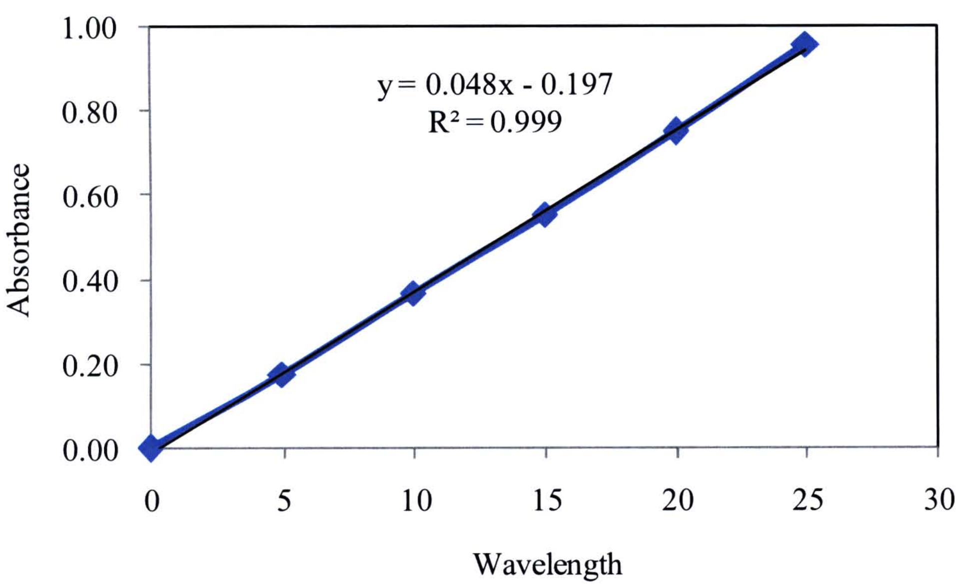



**Figure 71 calibration curve of Indomethacin**

# BIOGRAPHY

# BIOGRAPHY

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Supachai Mekkapat, Chokchai Banditnopparat and Metha Rutnakornpituk. (2007). Dispersion of magnitite nanoparticles stabilized with methoxy poly(ethylene glycol)-polyester block copolymer in aqueous solotion : effect of copolymer composition and its molecular weight. In **the Congress on Science and Tecchnology of thailand (STT 33).** Nakhonsithammarat: Walailak University.

Supachai Mekkapat and Metha Rutnakornpituk. (2009). Aqueous ferrofluid of bilayer-surface magnetic nanoparticles. In **the Pure and Applied Chemistry International Conference (PACCON).** Phitsanulok: Naresuan University.

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Supachai Mekkapat and Metha Rutnakornpituk. (2009). Methoxy Poly(ethylene **glycol)-Polyester Copolymer as Iron Oxide Nanoparticle. In Dispersants. The International Congress for Innovation in Chemistry (PERCH-CIC Congress VI).** Pattaya: Jomtien palm beach hotel & resort.